

- **Poor Prognosis:** BCR-ABL1 fusion (Philadelphia chromosome), MLL rearrangements, hypodiploidy.

#### 5. Response to Initial Therapy:

- **Standard Risk:** Rapid early response, minimal residual disease (MRD) negative.
- **High Risk:** Slow response, MRD positive after induction therapy.

#### 6. Central Nervous System (CNS) Involvement:

- **Standard Risk:** No CNS involvement.
- **High Risk:** CNS involvement at diagnosis.

#### 7. Testicular Involvement (in males):

- **High Risk:** Presence of testicular involvement at diagnosis.

#### 8. Ethnicity and Race:

- Certain ethnic and racial groups may have different risk profiles, although this is a less definitive factor compared to others.

#### 9. Other Clinical Features:

- **High Risk:** Features like a large mediastinal mass in T-cell ALL.

| Risk Factor                   | Standard Risk                    | High Risk                                         | Notes                                                                                |
|-------------------------------|----------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------|
| <b>Age at Diagnosis</b>       | 1-9 years                        | <1 year or >10 years                              | Age is a significant prognostic factor in ALL.                                       |
| <b>WBC Count at Diagnosis</b> | <50,000/ $\mu$ L                 | >50,000/ $\mu$ L                                  | High WBC count is associated with poorer prognosis.                                  |
| <b>Immunophenotype</b>        | B-cell ALL                       | T-cell ALL                                        | B-cell ALL generally has a better prognosis.                                         |
| <b>Genetic Abnormalities</b>  | Hyperdiploidy, ETV6-RUNX1 fusion | BCR-ABL1 fusion, MLL rearrangements, Hypodiploidy | Genetic markers play a crucial role in determining prognosis and treatment approach. |
| <b>Response to Therapy</b>    | Rapid response, MRD negative     | Slow response, MRD positive                       | Minimal residual disease (MRD) status post-induction is a                            |

|                                |                               |                                            |                                                                    |
|--------------------------------|-------------------------------|--------------------------------------------|--------------------------------------------------------------------|
|                                |                               |                                            | key prognostic indicator.                                          |
| <b>CNS Involvement</b>         | No involvement                | Presence at diagnosis                      | CNS involvement at diagnosis indicates a higher risk.              |
| <b>Testicular Involvement</b>  | Not applicable                | Presence at diagnosis (in males)           | Testicular involvement is a marker of high risk in male patients.  |
| <b>Ethnicity and Race</b>      | Variable                      | Variable                                   | Certain ethnic and racial groups may have different risk profiles. |
| <b>Other Clinical Features</b> | Absence of high-risk features | Large mediastinal mass in T-cell ALL, etc. | Additional clinical features can influence risk stratification.    |

### 10. b) Management of tumour lysis syndrome.

- ❖ Tumor Lysis Syndrome (TLS) is a potentially life-threatening oncological emergency that occurs when tumor cells release their contents into the bloodstream, typically in response to cancer treatment
- ❖ Effective management of TLS involves both preventive measures and active treatment strategies
- ❖ Management of TLS requires a multidisciplinary approach, with prompt recognition and treatment of metabolic abnormalities
- ❖ Prophylactic measures are crucial in high-risk patients, and continuous monitoring is essential for early detection and management of complications
- ❖ The goal is to prevent renal failure and severe electrolyte imbalances, thereby reducing morbidity and mortality associated with TLS.

#### Preventive Measures:

- **Risk Assessment:** Identify high-risk patients (e.g., those with high tumor burden or sensitive to treatment like lymphomas, acute leukemias).
- **Hydration:** Aggressive intravenous hydration to maintain urine output and reduce the concentration of serum electrolytes. In high risk cases it is even started 48 hours prior to the initiation of cancer chemotherapy.



- **Allopurinol or Rasburicase:** Prophylactic administration to prevent hyperuricemia. Rasburicase is preferred in high-risk patients.
- **Monitoring:** Frequent monitoring of renal function, electrolytes (potassium, calcium, phosphate), and uric acid levels.

### **Active Treatment Strategies:**

#### **1. Hyperkalemia:**

- **Mild to Moderate:** Sodium polystyrene sulfonate (Kayexalate), diuretics, oral/rectal bicarbonate.
- **Severe:** Insulin with glucose, calcium gluconate (for cardiac protection), beta-agonists, dialysis in refractory cases.

#### **2. Hyperphosphatemia and Hypocalcemia:**

- **Phosphate Binders:** Sevelamer, calcium acetate.
- **Avoid Calcium Supplements:** Unless symptomatic hypocalcemia.
- **Dialysis:** Considered if severe and refractory to medical management.

#### **3. Hyperuricemia:**

- **Rasburicase:** Especially in high-risk patients or those with established hyperuricemia.
- **Allopurinol:** In lower-risk patients or as prophylaxis.

#### **4. Acute Kidney Injury:**

- **Maintain Urine Output:** Diuretics if necessary.
- **Avoid Nephrotoxins:** NSAIDs, certain antibiotics.
- **Dialysis:** If indicated based on renal function and fluid overload.

#### **5. Monitoring and Supportive Care:**

- **Regular Monitoring:** Electrolytes, renal function, uric acid, and fluid balance.
- **Supportive Care:** Management of nausea, vomiting, and other symptoms.

#### **6. Dialysis:**

- **Indications:** Refractory hyperkalemia, hyperphosphatemia, significant renal impairment, or severe fluid overload.

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## Paper 3

### 1. a) Karyotype in Down's syndrome and its role in genetic counselling.

- ❖ Down syndrome, also known as trisomy 21, is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21
- ❖ Karyotyping in Down syndrome is fundamental for accurate diagnosis and essential in genetic counseling
- ❖ It helps in understanding the type of Down syndrome, assessing recurrence risks, and providing appropriate guidance and support to the families
- ❖ Genetic counseling is a vital component of comprehensive care, addressing both the medical and emotional aspects of the condition.

#### **Karyotype in Down Syndrome:**

##### 1. **Standard Trisomy 21:**

- Accounts for about 95% of cases.
- Karyotype: 47,XX,+21 in females or 47,XY,+21 in males.
- Caused by nondisjunction during meiosis, leading to an extra chromosome 21.

##### 2. **Robertsonian Translocation:**

- Accounts for about 4% of cases.
- Karyotype: 46 chromosomes, but with an extra part of chromosome 21 attached to another chromosome (usually 14 or 22).
- This form can be inherited.

##### 3. **Mosaic Down Syndrome:**

- Accounts for about 1% of cases.
- Karyotype: Mixture of normal cells (46,XX or 46,XY) and cells with an extra chromosome 21 (47,XX,+21 or 47,XY,+21).
- Results from nondisjunction occurring in one of the initial cell divisions after fertilization.

#### **Role in Genetic Counseling:**

##### 1. **Confirmation of Diagnosis:**



- Karyotyping is essential for confirming the diagnosis of Down syndrome, especially in cases where the clinical presentation is ambiguous.

## 2. **Determining the Type of Down Syndrome:**

- Identifying whether the Down syndrome is due to standard trisomy, Robertsonian translocation, or mosaicism has implications for recurrence risk and genetic counseling.

## 3. **Recurrence Risk:**

- **Standard Trisomy 21:** Usually a random event with a low recurrence risk unless the mother is of advanced maternal age.
- **Robertsonian Translocation:** If a parent is a carrier of a balanced translocation, the recurrence risk can be significantly higher.
- **Mosaic Down Syndrome:** Generally considered a random event with a low recurrence risk.

## 4. **Family Planning:**

- Genetic counseling provides information on the likelihood of Down syndrome occurring in future pregnancies and discusses options like prenatal testing.

## 5. **Support and Resources:**

- Counselors provide information about the condition, what to expect, and resources for support and care.

## 6. **Psychological Support:**

- Counseling helps families cope with the emotional aspects of the diagnosis and plan for the child's needs.

## 7. **Implications for Siblings and Extended Family:**

- In cases of translocation Down syndrome, siblings and other family members may opt for genetic testing to determine if they are carriers.

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## 1. b) Principles of gene therapy.

- ❖ Gene therapy is a groundbreaking medical intervention that involves modifying or manipulating the genetic material within a person's cells to treat or prevent disease
- ❖ The principles of gene therapy are rooted in molecular biology, genetics, and clinical medicine
- ❖ Gene therapy represents a frontier in medical science, offering potential cures for previously untreatable diseases
- ❖ Its principles encompass a broad range of scientific and ethical considerations, emphasizing the need for precision, safety, and patient-specific approaches
- ❖ As research progresses, gene therapy continues to evolve, promising transformative impacts on healthcare.

### 1. Target Identification and Validation:

- **Disease-Specific Genes:** Identifying and validating the specific genes involved in a disease.
- **Pathophysiological Understanding:** Understanding how these genes contribute to the disease process.

### 2. Gene Delivery Methods:

- **Vectors:** Utilizing vectors (like viruses) to deliver therapeutic genes to the patient's cells.
- **Non-Viral Methods:** Electroporation, liposomes, and nanoparticles.

### 3. Gene Modification Techniques:

- **Gene Addition:** Introducing a new gene to replace a missing or defective one.
- **Gene Silencing:** Using techniques like RNA interference to silence a harmful gene.
- **Gene Editing:** CRISPR-Cas9 and other technologies to precisely edit the genome.

### 4. Target Cells:

- **Somatic Cells:** Modifying somatic (body) cells, affecting only the patient.
- **Germ Cells:** Germ line gene therapy affects future generations (currently not ethically or legally accepted in humans).

### 5. Route of Administration:



- **In Vivo:** Directly delivering the gene therapy to the patient.
- **Ex Vivo:** Modifying the patient's cells outside the body and then reintroducing them.

#### 6. Safety and Ethical Considerations:

- **Minimizing Risks:** Ensuring the safety of the vectors and the gene therapy.
- **Ethical Concerns:** Addressing concerns about genetic enhancement, germ line therapy, and consent.

#### 7. Regulatory Compliance:

- **Clinical Trials:** Adhering to rigorous clinical trial phases to ensure safety and efficacy.
- **Approval Processes:** Complying with regulatory bodies like the FDA or EMA.

#### 8. Immunogenicity and Host Response:

- **Immune Response:** Managing the body's immune response to the vectors or the modified cells.
- **Long-term Effects:** Monitoring for potential long-term effects or complications.

#### 9. Durability and Control of Gene Expression:

- **Long-term Expression:** Ensuring that the therapeutic effect is sustained over time.
- **Regulated Expression:** Controlling the level and timing of gene expression.

#### 10. Personalized Medicine:

- **Individual Tailoring:** Customizing gene therapy based on the patient's genetic makeup and specific disease characteristics.

| Disease/Condition                       | Status of Gene Therapy      | Notes                                                                            |
|-----------------------------------------|-----------------------------|----------------------------------------------------------------------------------|
| Severe Combined Immunodeficiency (SCID) | Approved/In Clinical Trials | Gene therapy is particularly effective for certain types of SCID, like ADA-SCID. |
| Hemophilia                              | Clinical Trials             | Trials focus on providing functional copies of clotting factor genes.            |
| Cystic Fibrosis                         | Research/Early Trials       | Challenges include efficient gene delivery to the lungs.                         |
| Duchenne Muscular Dystrophy (DMD)       | Clinical Trials             | Strategies involve exon skipping or providing functional dystrophin genes.       |

|                                           |                                                |                                                                               |
|-------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------|
| <b>Beta-Thalassemia</b>                   | Approved (in specific regions)/Clinical Trials | Gene therapy aims to correct or replace the defective hemoglobin gene.        |
| <b>Sickle Cell Disease</b>                | Clinical Trials                                | Similar approach to beta-thalassemia, focusing on hemoglobin gene correction. |
| <b>Spinal Muscular Atrophy (SMA)</b>      | Approved                                       | Gene replacement therapy for the missing or defective SMN1 gene.              |
| <b>Leber's Congenital Amaurosis (LCA)</b> | Approved                                       | Targeting retinal gene defects to restore vision or halt progression.         |
| <b>Batten Disease</b>                     | Clinical Trials                                | Focus on replacing defective lysosomal enzymes or genes.                      |
| <b>Metachromatic Leukodystrophy (MLD)</b> | Clinical Trials                                | Gene therapy aims to replace the defective ARSA gene.                         |
| <b>Adrenoleukodystrophy (ALD)</b>         | Clinical Trials                                | Targeting ABCD1 gene mutations to prevent neurodegeneration.                  |
| <b>Hunter Syndrome (MPS II)</b>           | Clinical Trials                                | Focused on providing functional IDS enzyme gene.                              |
| <b>Sanfilippo Syndrome (MPS III)</b>      | Clinical Trials                                | Research on replacing or correcting the defective enzyme genes.               |

- **Evolving Field:** Gene therapy is a rapidly evolving field; new trials are constantly being initiated.
- **Regulatory Approvals:** Some therapies have received regulatory approval in certain regions but may not be globally available.
- **Individual Variability:** The effectiveness of gene therapy can vary based on individual genetic and disease factors.
- **Safety and Efficacy:** Ongoing research is focused on improving the safety and efficacy of these treatments.

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## 2. a) Differential diagnosis in a child with swelling of multiple joints for 6 weeks duration.

| <b>Differential Diagnosis</b>              | <b>Key Features</b>                                        | <b>Diagnostic Tests</b>             | <b>Notes</b>                                                         |
|--------------------------------------------|------------------------------------------------------------|-------------------------------------|----------------------------------------------------------------------|
| <b>Juvenile Idiopathic Arthritis (JIA)</b> | Chronic arthritis in one or more joints; morning stiffness | ANA, RF, Anti-CCP, ESR, CRP         | Most common cause of chronic arthritis in children; several subtypes |
| <b>Rheumatic Fever</b>                     | Migratory arthritis, carditis, chorea, erythema marginatum | Throat culture, ASO titer, ESR, CRP | History of recent streptococcal infection is crucial                 |



|                                           |                                                                    |                                                   |                                                                         |
|-------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------|-------------------------------------------------------------------------|
| <b>Systemic Lupus Erythematosus (SLE)</b> | Joint swelling, rash, renal involvement, hematologic abnormalities | ANA, Anti-dsDNA, Anti-Smith, complement levels    | Multi-system involvement; more common in adolescents                    |
| <b>Lyme Disease</b>                       | Arthritis, erythema migrans, flu-like symptoms                     | Lyme serology (ELISA, Western blot)               | History of tick exposure; endemic areas                                 |
| <b>Leukemia</b>                           | Bone pain, joint swelling, fatigue, pallor, bruising               | CBC with differential, bone marrow biopsy         | Hematologic malignancy; bone pain often mistaken for arthritis          |
| <b>Sarcoidosis</b>                        | Arthritis, uveitis, lung involvement, skin lesions                 | Chest X-ray, ACE levels, biopsy of affected organ | Rare in children; multi-system granulomatous disorder                   |
| <b>Inflammatory Bowel Disease (IBD)</b>   | Joint swelling, abdominal pain, diarrhea, weight loss              | Colonoscopy, fecal calprotectin, CRP, ESR         | Extraintestinal manifestations of Crohn's disease or ulcerative colitis |
| <b>Viral Arthritis</b>                    | Self-limited joint swelling, history of recent viral infection     | Viral serologies, PCR for specific viruses        | Often follows viral infections like parvovirus, hepatitis B             |
| <b>Henoch-Schönlein Purpura (HSP)</b>     | Palpable purpura, abdominal pain, renal involvement                | Urinalysis, renal function tests, skin biopsy     | Small vessel vasculitis; more common in younger children                |
| <b>Reactive Arthritis</b>                 | Arthritis following gastrointestinal or genitourinary infection    | Stool culture, HLA-B27, ESR, CRP                  | Can follow infections like Salmonella, Yersinia, Chlamydia              |
| <b>Familial Mediterranean Fever (FMF)</b> | Recurrent fever, serositis, arthritis, abdominal pain              | Genetic testing for MEFV gene mutations           | Periodic fever syndrome; more common in certain ethnic groups           |

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## 2. b) Classification and diagnostic criteria of JIA.

### Diagnostic Criteria for JIA:

Inclusion Criteria:

- **Age of Onset:** Less than 16 years.
- **Duration of Arthritis:** Arthritis in one or more joints lasting for at least 6 weeks.

- **Exclusion of Other Conditions:** Conditions like infections, trauma, malignancy, or other rheumatic diseases must be excluded.

### Criteria for the Classification of Juvenile Idiopathic Arthritis:

- Age at onset: <16 yrs.
  - Duration of disease: >6 weeks
  - Arthritis- swelling or effusion, or the presence of 2 or more of the following signs in >1 joint:
    - limitation of range of motion,
    - tenderness or pain on motion,
    - increased heat
  - Onset type defined by type of articular involvement in the first 6 months after onset:
  - Polyarthritis: >5 inflamed joints
  - Oligoarthritis: <4 inflamed joints
  - Systemic-onset disease: arthritis with rash and a characteristic quotidian fever
  - Exclusion of other forms of juvenile arthritis
- 
- **Epidemiology:** No sex predominance in systemic JIA, but more girls than boys are affected in both oligoarticular (3:1) and polyarticular (5:1) JIA. The peak age at onset varies for different types.
  - **Etiology:** The etiology and pathogenesis of JIA are largely unknown. It represents a heterogeneous group of disorders sharing the clinical manifestation of arthritis. Genetic factors play a role, but the genetic component is complex.

### Subtypes and Additional Criteria:

1. **Oligoarticular JIA:** Involvement of up to 4 joints during the first 6 months of disease.
  - **ANA Positive:** Increased risk of developing uveitis.
2. **Polyarticular JIA (RF Negative):** Involvement of 5 or more joints during the first 6 months; Rheumatoid Factor (RF) negative.
3. **Polyarticular JIA (RF Positive):** Involvement of 5 or more joints during the first 6 months; RF positive on at least two occasions at least 3 months apart.
4. **Systemic JIA:** Arthritis with or preceded by at least 2 weeks of daily fever; plus one or more of the following:



- Evanescent (non-fixed) erythematous rash
  - Generalized lymph node enlargement
  - Hepatomegaly or splenomegaly
  - Serositis
5. **Enthesitis-Related JIA:** Arthritis and enthesitis, or arthritis or enthesitis with at least two of the following:
- Sacroiliac joint tenderness
  - Inflammatory lumbosacral pain
  - Presence of HLA-B27 antigen
  - Acute (symptomatic) anterior uveitis
  - History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
6. **Psoriatic JIA:** Arthritis and psoriasis, or arthritis and at least two of the following:
- Dactylitis
  - Nail pitting or onycholysis
  - Psoriasis in a first-degree relative

#### Laboratory Tests:

- **Rheumatoid Factor (RF):** For classification into RF-positive or RF-negative subtypes.
- **Anti-Nuclear Antibody (ANA):** For risk stratification, especially in oligoarticular JIA.
- **HLA-B27:** In cases of suspected enthesitis-related JIA.

#### Imaging:

- **X-ray:** To assess joint damage.
- **MRI:** For early detection and evaluation of joint and soft tissue involvement.

#### Summary of Classification of JIA:

1. **Oligoarticular JIA:**

- Involves 1 to 4 joints during the first 6 months.
  - Two subtypes: Persistent (affects  $\leq 4$  joints throughout) and Extended (affects  $>4$  joints after the first 6 months).
2. **Polyarticular JIA (Rheumatoid Factor Negative):**
- Involves 5 or more joints in the first 6 months.
  - Rheumatoid Factor (RF) is negative.
3. **Polyarticular JIA (Rheumatoid Factor Positive):**
- Involves 5 or more joints in the first 6 months.
  - RF is positive, similar to adult rheumatoid arthritis.
4. **Systemic JIA:**
- Characterized by arthritis and systemic features like fever, rash, serositis, hepatosplenomegaly, and lymphadenopathy.
5. **Psoriatic JIA:**
- Arthritis and psoriasis or arthritis plus at least two of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative.
6. **Enthesitis-Related Arthritis (ERA):**
- Arthritis and enthesitis (inflammation of tendon insertions) or arthritis or enthesitis with at least two of the following: sacroiliac joint tenderness, inflammatory spinal pain, HLA-B27 positivity, family history of HLA-B27 associated disease.
7. **Undifferentiated JIA:**
- Arthritis that does not fit into any of the above categories or fits into more than one.

### Classification and Features of Juvenile Idiopathic Arthritis (JIA) / ILAR classification of juvenile idiopathic arthritis

| Classification of JIA | Definition and Criteria                                                                    | Clinical Features             | Exclusions and Special Notes                             |
|-----------------------|--------------------------------------------------------------------------------------------|-------------------------------|----------------------------------------------------------|
| <b>Systemic JIA</b>   | Arthritis in $\geq 1$ joint with fever of at least 2 weeks. Accompanied by $\geq 1$ of the | Fever, rash, lymphadenopathy, | Excludes psoriasis, HLA-B27 positive arthritis after 6th |



|                                           |                                                                                                                                                                                  |                                                                                                |                                                                                                                                                                                         |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                           | following: evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly or splenomegaly, serositis.                                                            | hepatosplenomegaly, serositis.                                                                 | birthday, ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, Reiter syndrome, acute anterior uveitis, IgM RF on at least 2 occasions at least 3 months apart. |
| <b>Oligoarthritis</b>                     | Arthritis affecting $\leq 4$ joints.                                                                                                                                             | Typically affects large joints like knees; may have uveitis.                                   | -                                                                                                                                                                                       |
| <b>Polyarthritis</b>                      | Arthritis affecting $\geq 5$ joints.                                                                                                                                             | Affects both small and large joints; may be Rheumatoid Factor positive or negative.            | -                                                                                                                                                                                       |
| <b>Psoriatic Arthritis</b>                | Arthritis with psoriasis or a family history of psoriasis.                                                                                                                       | Skin lesions, dactylitis, and nail pitting may be present.                                     | -                                                                                                                                                                                       |
| <b>Enthesitis-Related Arthritis (ERA)</b> | Arthritis with enthesitis or arthritis or enthesitis with at least two other features such as sacroiliac joint tenderness, inflammatory lumbosacral pain, or HLA-B27 positivity. | Lower back pain, heel pain, joint pain. May also have acute anterior uveitis.                  | Excludes rheumatoid factor-positive arthritis and other forms of JIA.                                                                                                                   |
| <b>Undifferentiated Arthritis</b>         | Arthritis that does not fit into the other categories or fits into more than one of the above categories.                                                                        | Varies; does not meet criteria for other subtypes or meets criteria for more than one subtype. | -                                                                                                                                                                                       |

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### 3. a) Sexual Maturity Rating in girls.

| Tanner Stage | Breast Development                                                                                                                | Pubic Hair Development                                                                                             | Description                                                                          |
|--------------|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| Stage 1      | Prepubertal: No glandular tissue; areola follows the skin contours of the chest.                                                  | Prepubertal: No pubic hair; vellus hair is similar to that on the abdomen.                                         | Initial phase indicating the onset of puberty is imminent.                           |
| Stage 2      | Breast bud stage: Small mound of breast and nipple develops; the areola widens.                                                   | Sparse growth of long, slightly pigmented, downy hair, straight or slightly curled, mainly along the labia.        | Early development of breast and pubic hair, indicating the start of puberty.         |
| Stage 3      | Further enlargement of breast and areola; no separation of their contours.                                                        | Darker, coarser, and more curled hair, spreading sparsely over the pubic area.                                     | Continued development of breast and pubic hair, showing progression through puberty. |
| Stage 4      | Areola and nipple form a secondary mound above the level of the breast.                                                           | Adult-type hair but covering a smaller area than in adults; no spread to medial thigh.                             | Advanced development with distinct changes in breast and pubic hair pattern.         |
| Stage 5      | Mature stage: Breast reaches final adult size; areola returns to the contour of the surrounding breast, with a projecting nipple. | Adult in quantity and type, with horizontal distribution; spread to medial thigh but not up towards the umbilicus. | Completion of puberty with fully developed breasts and adult pattern of pubic hair.  |

#### Notes:

- **Variability:** There is considerable individual variation in the timing and progression of these stages.
- **Clinical Use:** These stages are used for assessing and monitoring the physical development of adolescents.



- **Sensitivity:** The assessment should be conducted with respect for the child's privacy and comfort.

### 3. b) Define precocious puberty and its causes.

Precocious puberty refers to the onset of physical and hormonal signs of pubertal development at an age earlier than the accepted lower age limit for the population. In boys, precocious puberty is generally defined as the onset of pubertal changes before the age of 9.5 years. For girls 8 years of age.

#### *Causes of Precocious Puberty in Girls:*

| Cause                                              | Type       | Description                                                                         |
|----------------------------------------------------|------------|-------------------------------------------------------------------------------------|
| Central Nervous System (CNS) Abnormalities         | Central    | Tumors (e.g., astrocytoma, glioma), hydrocephalus, trauma, infection, or radiation. |
| Idiopathic                                         | Central    | No identifiable cause; most common in girls.                                        |
| Hypothalamic Hamartoma                             | Central    | Benign tumor that can prematurely activate the hypothalamic-pituitary-gonadal axis. |
| McCune-Albright Syndrome                           | Peripheral | Genetic disorder causing bone, skin changes, and hormonal imbalances.               |
| Hypothyroidism                                     | Peripheral | Rarely, severe untreated hypothyroidism can lead to precocious puberty.             |
| Ovarian Tumors/Cysts                               | Peripheral | Certain tumors or cysts can produce estrogen, leading to early puberty.             |
| Adrenal Gland Disorders                            | Peripheral | Conditions like congenital adrenal hyperplasia causing excess hormone production.   |
| Exogenous Hormones                                 | Peripheral | Exposure to external sources of estrogens.                                          |
| Familial Gonadotropin-Independent Sexual Precocity | Peripheral | Rare genetic conditions causing early puberty.                                      |

#### *Causes of Precocious Puberty in Boys:*

| Cause             | Type    | Description                                                          |
|-------------------|---------|----------------------------------------------------------------------|
| CNS Abnormalities | Central | Tumors, hydrocephalus, trauma, infection, or radiation to the brain. |
| Idiopathic        | Central | No identifiable cause; less common in boys than in girls.            |

|                                                                  |            |                                                                   |
|------------------------------------------------------------------|------------|-------------------------------------------------------------------|
| <b>Hypothalamic Hamartoma</b>                                    | Central    | Benign tumor causing early puberty.                               |
| <b>Testicular Tumors</b>                                         | Peripheral | Rare, but can secrete hormones triggering puberty.                |
| <b>Adrenal Gland Disorders</b>                                   | Peripheral | Conditions like congenital adrenal hyperplasia.                   |
| <b>McCune-Albright Syndrome</b>                                  | Peripheral | Less common in boys, causes early puberty among other symptoms.   |
| <b>Exogenous Hormones</b>                                        | Peripheral | Exposure to external androgens.                                   |
| <b>Familial Male-Limited Precocious Puberty (Testotoxicosis)</b> | Peripheral | Rare genetic disorder causing early puberty in boys.              |
| <b>Hepatic Disorders</b>                                         | Peripheral | Rarely, liver diseases can be associated with precocious puberty. |

- **Variability in Causes:** The causes of precocious puberty can vary widely between individuals, and in many cases, the exact cause may remain unknown, especially in girls.
- **Importance of Evaluation:** A thorough evaluation including history, physical examination, and appropriate investigations is essential to determine the cause.
- **Treatment and Management:** Treatment depends on the cause and may include medications to delay further pubertal development, especially in cases of central precocious puberty.

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#### 4. a) Approach to a suspected primary immunodeficiency disorder.

##### General Approach

A child with suspected immune dysfunction requires a comprehensive evaluation that includes a detailed history, physical examination, and laboratory tests. The approach is guided by the type of immunodeficiency suspected: B-cell, T-cell, macrophage dysfunction, or congenital syndromes.

##### B-Cell Defect (Humoral Immunodeficiency)

- **Clinical Indicators**
  - Recurrent bacterial infections of the upper and lower respiratory tracts, recurrent skin infections, meningitis, osteomyelitis.
- **Causative Agents**
  - Encapsulated bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Neisseria meningitidis*.



- **Additional Signs**
  - Paralysis after vaccination with live-attenuated poliovirus.
- **Laboratory Findings**
  - Reduced levels of immunoglobulins.

### ***T-Cell Defect (Combined Immunodeficiency)***

- **Clinical Indicators**
  - Systemic illness after vaccination with live viruses or BCG, unusual life-threatening complications after benign viral infections.
- **Additional Signs**
  - Chronic oral candidiasis after age 6 months, chronic mucocutaneous candidiasis, graft-versus-host disease after blood transfusion.
- **Laboratory Findings**
  - Reduced lymphocyte counts for age, low levels of immunoglobulins, absence of lymph nodes and tonsils, small thymus.
- **Systemic Indicators**
  - Chronic diarrhea, failure to thrive, recurrent infections with opportunistic organisms.

### ***Macrophage Dysfunction***

- **Clinical Indicators**
  - Disseminated atypical mycobacterial infection, recurrent Salmonella infection.
- **Additional Signs**
  - Fatal infection after BCG vaccination.

### ***Congenital Syndromes with Immunodeficiency***

- **Ataxia-Telangiectasia**
  - Ataxia, telangiectasia.
- **Autoimmune Polyglandular Syndrome**
  - Hypofunction of one or more endocrine organs, chronic mucocutaneous candidiasis.
- **Cartilage-Hair Hypoplasia**

- Short-limbed dwarfism, sparse hair, neutropenia.
- **Wiskott-Aldrich Syndrome**
  - Thrombocytopenia, male gender, eczema.
- **Chédiak–Higashi Syndrome**
  - Oculocutaneous albinism, nystagmus, recurrent bacterial infections, peripheral neuropathies.
- **DiGeorge Syndrome (22q Deletion Syndrome)**
  - Unusual facies, heart defect, hypocalcemia.

### **Asplenia-Related Indicators**

- **Clinical Indicators**
  - Heterotaxia, complex congenital heart disease, Howell-Jolly bodies on blood smear, sickle cell anemia.

### **Diagnostic testing algorithm for primary immunodeficiency diseases**

- **Common Clinical Scenarios:**
  - Bacterial infections: Conditions like sepsis, meningitis, and pneumonia.
  - Mycobacterial infections: Notably, Mycobacterium infections other than the typical tuberculosis-causing strains.
  - Viral infections: Emphasizing infants with severe or unusual viral infections of the respiratory system.
  - Fungal infections: Includes infections from Candida and molds.
- **Diagnostic Flow:**
  - **Initial Tests:**
    - CBC differential: To get a full profile of blood cell types.
    - Serum enumeration of immunoglobulins: Checking levels of IgG, IgA, IgM, and IgE.
    - DHR (Dihydrorhodamine test): To check the burst activity of neutrophils.
    - CH50: Total complement activity test.
  - **Suspected Areas:**



- If the issue is suspected with the T-cell function, consider sequencing the T-cell receptor.
- If levels of immunoglobulins are specifically deficient or non-existent, HIV should be considered.

### ***Initial workup and follow-up studies of patients with suspected immunodeficiency***

- ***Initial Investigations:***

- Clinical examination: A comprehensive history including family history; and physical assessment.
- CBC with differential: A thorough blood count checking for all cell types.
- Culture findings: Checking for specific pathogens.
- Serum immunoglobulin levels: Levels of IgG, IgM, IgA, and IgE are examined.
- Specific antibody titers: Measuring the immune system's response to specific pathogens.
- Complement system evaluation: CH50 and AH50 tests to check for any abnormalities.

- ***Depending on Findings, Further Steps:***

- ***Suspect Phagocyte Defect:***

- Tests for oxidative burst: Mainly the dihydrorhodamine (DHR) test.
- Flow cytometry for specific markers: This includes markers like CD18 or LAD1/CD11b and CD11c (LAD2).
- Further studies: Neutrophil chemotaxis assays and tests to check IL-12 or interferon-gamma receptor expression.

- ***Suspect Humoral (antibody-producing cells) Defect:***

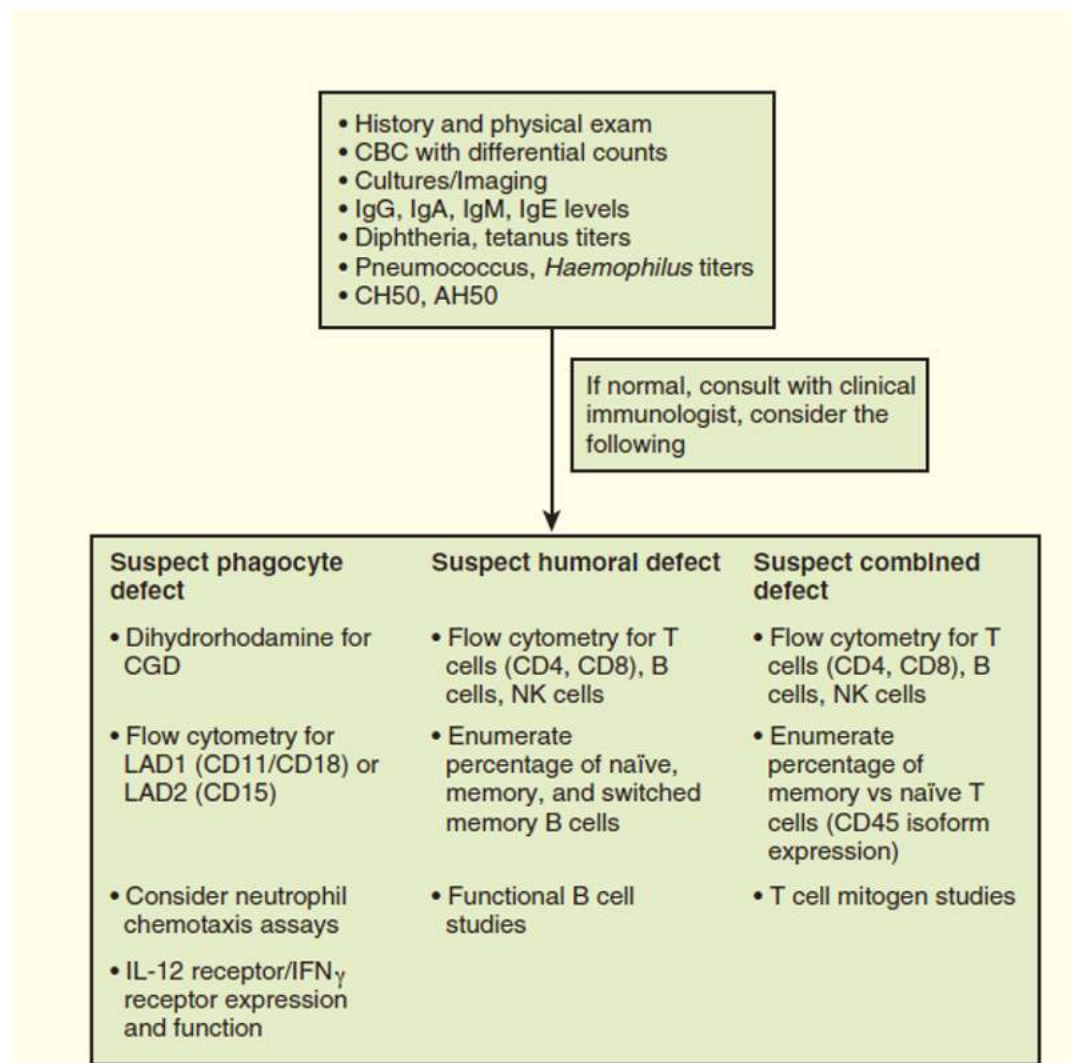
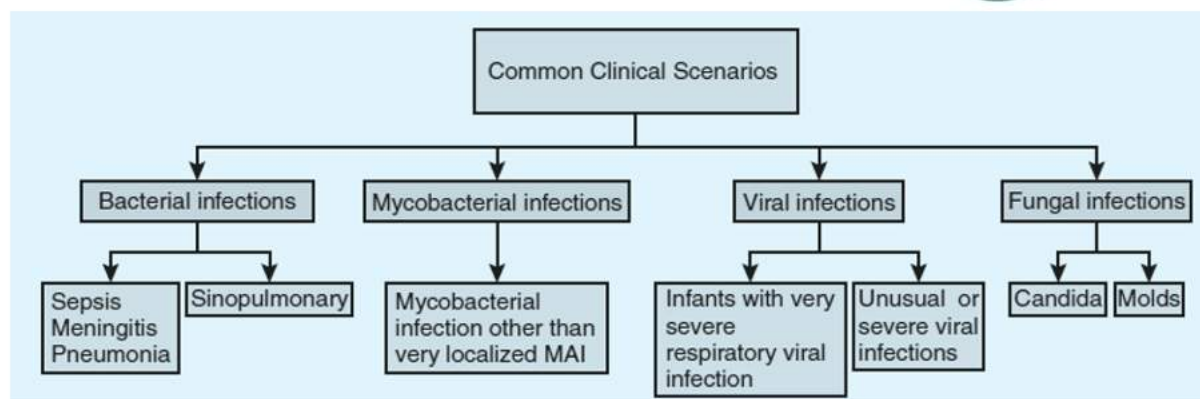
- Flow cytometry: Checking for B-cell markers such as CD19, CD20, CD21, and CD81.
- Analysis for immunoglobulins: Mainly memory B cells and switched memory B cells.
- Functional B-cell studies: To assess the full capabilities of the B-cells.



- **Suspect Combined Immunodeficiency:**
  - Flow cytometry for T cells: Looking at markers such as CD3, CD4, CD8, CD45RA, and CD45RO.
  - Studies on T cell function: Checking the proliferative response to mitogens.
  - T-cell mitogen studies: To see how T-cells respond to stimuli.







#### 4. b) Clinical features and laboratory findings in primary B cell immunodeficiency.

*Clinical Features of Primary B Cell Immunodeficiencies:*

1. **Delayed Onset of Symptoms:**

- Typically manifest after 6 months as maternal IgG wanes.
- Early presentation may occur in severe cases.

2. **Recurrent Bacterial Infections:**

- Predominantly by encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*).
- Common sites: respiratory tract (sinusitis, otitis media, bronchitis, pneumonia), gastrointestinal tract.

3. **Enteroviral Infections:**

- X-linked agammaglobulinemia (XLA) patients are particularly vulnerable to chronic enteroviral meningoencephalitis.

4. **Gastrointestinal Complications:**

- Chronic diarrhea, malabsorption, giardiasis.
- Increased risk of inflammatory bowel disease-like conditions.

5. **Autoimmune Phenomena:**

- Autoimmune cytopenias (hemolytic anemia, thrombocytopenia).
- Arthritis, dermatomyositis-like syndrome.

6. **Atopic Disorders:**

- Eczema, allergic rhinitis, asthma.
- Paradoxical given the impaired antibody response.

7. **Growth and Development:**

- Failure to thrive due to chronic infections and gastrointestinal issues.

8. **Increased Risk of Malignancy:**

- Particularly lymphomas and gastric cancer.

**Laboratory Findings in Primary B Cell Immunodeficiency:**

1. **Serum Immunoglobulin Levels:**

- Markedly reduced or absent IgG, IgA, IgM.
- In XLA, near-complete absence of all immunoglobulin isotypes.

2. **Vaccine Response:**



- Poor or absent response to polysaccharide and protein antigens.
- Assessment post-immunization is crucial for diagnosis.

3. ***Lymphocyte Immunophenotyping:***

- Profound reduction or absence of CD19+ B cells.
- Normal T cell numbers; may have functional abnormalities secondary to lack of B cell interaction.

4. ***Genetic Analysis:***

- Identification of specific mutations (e.g., BTK gene in XLA).
- Genetic counseling is important for family planning.

5. ***Bone Marrow Analysis:***

- Lack of mature B cells; maturation arrest at the pre-B cell stage in XLA.

6. ***Isohemagglutinin Titers:***

- Absent or very low; indicative of poor response to environmental antigens.

***Specific Disorders:***

1. ***X-Linked Agammaglobulinemia (XLA):***

- Caused by mutations in the BTK gene.
- Presents with recurrent bacterial infections post 6-months age.

2. ***Common Variable Immunodeficiency (CVID):***

- Heterogeneous; diagnosis often in late childhood or adult life.
- Variable clinical presentation: infections, autoimmunity, malignancy.

3. ***Selective IgA Deficiency:***

- Most common; often asymptomatic.
- Can present with sinopulmonary infections, allergies, autoimmune diseases.

4. ***Hyper IgM Syndromes:***

- Normal/elevated IgM with low IgG, IgA.
- Susceptibility to opportunistic infections.

5. ***Transient Hypogammaglobulinemia of Infancy:***

- Delayed maturation of B cell function.
- Typically resolves by age 2-4 years.

| B Cell Disorder                                   | Clinical Features                                                                                                                                                                       | Laboratory Findings                                                                                                      | Management                                                                                                                        |
|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| <b>X-Linked Agammaglobulinemia (XLA)</b>          | Recurrent bacterial infections post 6 months (sinusitis, otitis media, pneumonia).<br>Enteroviral infections.<br>Autoimmune diseases are rare.<br>Growth delay possible.                | Absent or very low B cells (CD19+).<br>Markedly reduced/absent IgG, IgA, IgM.<br>Mutation in BTK gene.                   | Regular immunoglobulin replacement therapy.<br>Prophylactic antibiotics for recurrent infections.<br>Genetic counseling.          |
| <b>Common Variable Immunodeficiency (CVID)</b>    | Variable onset, often in late childhood/adulthood.<br>Recurrent bacterial infections.<br>Autoimmune manifestations.<br>Increased risk of malignancy.<br>Gastrointestinal complications. | Low IgG and IgA, sometimes IgM.<br>Poor vaccine response.<br>Normal or low B cell numbers.<br>Exclusion of other causes. | Immunoglobulin replacement.<br>Management of autoimmune and gastrointestinal complications.<br>Regular monitoring for malignancy. |
| <b>Selective IgA Deficiency</b>                   | Often asymptomatic.<br>Recurrent sinopulmonary infections.<br>Association with allergies and autoimmune diseases.<br>Anaphylactic reactions to blood products containing IgA.           | Isolated low/absent IgA.<br>Normal IgG, IgM levels.<br>Normal B cell count.                                              | Antibiotic therapy for infections.<br>Monitoring for associated conditions.<br>Education about blood product reactions.           |
| <b>Hyper IgM Syndromes</b>                        | Susceptibility to opportunistic infections.<br>Neutropenia, lymphoid hyperplasia.<br>Autoimmune disorders.<br>Increased risk of malignancy.                                             | Elevated IgM.<br>Low IgG, IgA.<br>CD40/CD40L mutations (in some types).<br>Normal/elevated B cell count.                 | Immunoglobulin replacement.<br>Prophylactic antibiotics.<br>Hematopoietic stem cell transplantation in severe cases.              |
| <b>Transient Hypogammaglobulinemia of Infancy</b> | Recurrent infections in infancy (respiratory, gastrointestinal).<br>Typically self-resolves by age 2-4 years.                                                                           | Low IgG with normal IgM, IgA.<br>Delayed maturation of B cell function.<br>Normal B cell count.                          | Usually self-limiting.<br>Antibiotic therapy for infections.                                                                      |



|  |  |  |                                             |
|--|--|--|---------------------------------------------|
|  |  |  | Immunoglobulin replacement in severe cases. |
|--|--|--|---------------------------------------------|

- **Genetic Counseling:** Important for family planning and understanding the hereditary nature of some of these disorders.
- **Lifelong Management:** Most of these disorders require ongoing treatment and health monitoring.

### Management Strategies:

1. **Immunoglobulin Replacement Therapy:**
  - Mainstay for XLA, CVID.
  - Prevents most bacterial infections.
2. **Prophylactic Antibiotics:**
  - For recurrent bacterial infections.
3. **Management of Autoimmune Complications:**
  - Corticosteroids, immunosuppressants as needed.
4. **Regular Monitoring:**
  - For early detection of malignancies and assessment of organ function.
5. **Patient and Family Education:**
  - Understanding the disease, treatment adherence, and infection prevention strategies.

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## 5. a) Diagnosis of enteric fever.

### Epidemiology and Risk Factors:

- Prevalent in low and middle-income countries.
- Common in returning travelers and migrants from endemic areas.
- Increased risk with poor sanitation, hygiene, and contaminated water.
- More common in children and young adults; in travelers, adults are more frequently affected.

- Use of proton pump inhibitors increases susceptibility.

### Clinical Presentation:

- Gradual onset of fever, peaking at 39-40°C in a week.
- Abdominal symptoms: diarrhea, nausea, vomiting, and pain.
- Hepatitis and hepatomegaly more common in children under 5.
- Rose spots are rare but characteristic.
- Advanced stages may lead to a state of reduced responsiveness.

### Clinical Assessment:

#### 1. **Symptomatology:**

- Gradual onset of fever, which often increases in a stepwise manner.
- Headache, malaise, anorexia, and abdominal discomfort.
- In some cases, a rash (rose spots) on the trunk.

#### 2. **History Taking:**

- Travel history to endemic areas.
- Exposure to contaminated food or water.

#### 3. **Physical Examination:**

- Fever, relative bradycardia (fever without a proportional increase in heart rate).
- Abdominal tenderness, hepatosplenomegaly.
- In severe cases, signs of intestinal perforation or hemorrhage.

### Specific Laboratory Testing: (BASU – blood, antibody, stool, urine – weeks 1,2,3,4)

#### 1. **Blood Culture:**

- The gold standard for diagnosis, especially in the first week of illness.
- Sensitivity -61%, decreases as the disease progresses and with prior antibiotic use.

#### 2. **Bone Marrow Culture:**

- More sensitive than blood culture, but more invasive.



- Can remain positive even after antibiotic treatment has started.

### 3. **Stool and Urine Cultures:**

- Useful in the second week of illness.
- Stool cultures are often positive in the second and third weeks.

### 4. **Serology:**

- Widal test: Measures agglutinating antibodies against O and H antigens of Salmonella Typhi.
- Limited sensitivity and specificity, especially in endemic areas.
- Can be affected by prior vaccination and cross-reactivity with other Salmonella species.

### 5. **Molecular Diagnostics:**

- PCR assays for the detection of Salmonella Typhi and Paratyphi DNA.
- More rapid and sensitive, especially in early stages or after antibiotic initiation.

### 6. **Complete Blood Count (CBC):**

- Often shows leukopenia or a normal leukocyte count. Leukocytosis may indicate complications
- Anemia and thrombocytopenia in severe cases.

### 7. **Biochemical Tests:**

- Liver function tests may show elevated transaminases and bilirubin.

### **Imaging:**

#### 1. **Ultrasound or CT Scan:**

- May be indicated in complicated cases (e.g., intestinal perforation, ileal thickening).

### **Differential Diagnosis:**

- Other causes of fever, such as malaria, dengue, leptospirosis, and other bacterial infections, should be considered and ruled out based on clinical presentation and laboratory findings.

### **Differential Diagnosis:**

- Rule out malaria, dengue, scrub typhus, leptospirosis, brucellosis, influenza, chikungunya, and COVID-19 in endemic areas and returning travelers.

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### 5. b) Management of septic shock.

Septic shock in itself encompasses multiple forms of shock in varying degrees

- Hypovolemic: third spacing of fluids into the extracellular, interstitial space
- Distributive: early shock with decreased afterload
- Cardiogenic: depression of myocardial function by endotoxins

#### *Initial Identification and Continuous Evaluation*

Recognize signs of sepsis and septic shock, such as hypotension, altered mental status, and signs of poor perfusion like delayed capillary refill, mottled skin, and cold extremities

Continuously evaluate key parameters including heart rate, blood pressure, peripheral perfusion, respiratory pattern, level of consciousness, and urine output.

#### *Immediate Resuscitation and Preload Management*

- Initiate rapid fluid resuscitation with isotonic crystalloid solutions, guided by response and ongoing losses
- The initial bolus is typically 20 mL/kg, and this can be repeated to improve perfusion
- Employ central venous pressure (CVP) monitoring for fluid therapy beyond 60-80 ml/kg
- Fluid choice should be context-specific, ranging from crystalloids to colloids or blood products based on the etiology of the shock.

#### *Vasoactive and Inotropic Medications*

- If the patient remains hypotensive or shows signs of poor perfusion after fluid resuscitation, vasoactive medications like epinephrine or norepinephrine are indicated
- For myocardial dysfunction, consider adding an inotropic agent like dobutamine to improve cardiac output.

#### *Extensive Hemodynamic and Cardiovascular Monitoring*



- Utilize advanced hemodynamic monitoring techniques such as arterial blood-gas measurement, electrolyte and glucose monitoring, blood counts, coagulation profiles, continuous ECG, intra-arterial pressure, and central venous oxygen saturation (ScvO<sub>2</sub>) to guide resuscitation
- Focus on ensuring adequate blood flow and oxygen delivery to vital vascular beds, addressing heart rate, rhythm, and stroke volume, influenced by preload, contractility, and afterload.

| Drug             | Dose<br>( $\mu\text{g/kg/min}$ ) | Predominant site of action                                | Comment                                                                                                     |
|------------------|----------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Dopamine         | 0.5-5<br>5-10<br>>10             | Dopaminergic<br>$\beta_1$<br>$\alpha_1$                   | Vasodilator to renal and cerebral beds<br>Inotropic dose<br>Pressor dose                                    |
| Dobutamine       | 5-20                             | $\beta_1$ , $\beta_2$ , dopaminergic                      | Inotrope, weak chronotrope, mild<br>Vasodilator                                                             |
| Norepinephrine   | 0.05-1                           | $\alpha_1$ , $\beta_1$                                    | Strong vasoconstrictor and inotrope;<br>May cause splanchnic ischemia.                                      |
| Epinephrine      | 0.03-0.1<br>0.1-0.2<br>> 0.2     | $\beta$<br>$\alpha_1$ , $\beta_1$ , $\beta_2$<br>$\alpha$ | Inotrope<br>Inotrope and pressor effect<br>Vasoconstrictor, arrhythmogenic                                  |
| Dopexamine       | 0.5-6                            | $\beta_2$ , dopaminergic                                  | Inotrope, vasodilator, improves<br>splanchnic blood flow.                                                   |
| Phenylephrine    | 0.2-1                            | $\alpha_1$                                                | Vasoconstrictor                                                                                             |
| Milrinone        | 0.75-1                           |                                                           | Loading dose 50-75 mcg/kg iv;<br>shorter $t_{1/2}$ and less effect on platelets<br>as compared to amrinone. |
| Calcium chloride | 10-20 mg/kg                      |                                                           | Inotropy                                                                                                    |
| Nitroglycerine   | 0.75-1                           |                                                           | Venodilator                                                                                                 |
| Nitroprusside    | 10-20 mg/kg                      |                                                           | Vasodilator ( $A > V$ ).                                                                                    |

### **Antibiotic Therapy and Source Control**

- Administer empirical broad-spectrum antibiotics ideally within the first hour after recognition of septic shock
- Concurrently, identify and manage the source of infection, which may involve surgical intervention, drainage of abscesses, or removal of indwelling devices.

### **Therapeutic Goals and Reassessment**

- Aim for specific clinical endpoints such as normal pulses, capillary refill time < 2 sec, warm extremities, normal mental status, normal blood pressure, urine output > 1 ml/kg/hr, decreased serum lactate, reduced base deficit, and SvO<sub>2</sub> > 70%
- Regularly update the treatment plan based on the patient's clinical response, laboratory values, and monitoring data.

#### **Therapeutic endpoints in shock management**

Normal pulses  
 Capillary refill time < 2sec  
 Warm extremities  
 Normal mental status  
 Normal blood pressure  
 Urine output > 1 ml/kg/hr  
 Decreased serum lactate  
 Reduced base deficit  
 SvO<sub>2</sub> > 70%

#### **Afterload Management**

- Employ systemic vasodilators cautiously, especially in cardiogenic shock with increased systemic vascular resistance
- Invasive cardiovascular monitoring is advisable when using vasodilators.

#### **Pulmonary and Respiratory Support**

- Administer oxygen supplementation and assess its adequacy through continuous pulse oximetry and arterial blood gases
- Initiate mechanical ventilation for respiratory failure, utilizing lung-protective strategies and considering the use of neuromuscular blocking agents for severe ARDS.

#### **Renal and Metabolic Support**

- Place a Foley catheter for continuous urine output monitoring
- Employ diuretics for oliguria or anuria, and consider dialysis or continuous arteriovenous hemofiltration for acute renal failure
- Address metabolic acidosis and maintain serum sodium levels within normal ranges
- Correct hypoglycemia and hypocalcemia promptly.

#### **Gastrointestinal and Hematologic Support**

- Insert a nasogastric tube and employ measures to reduce the risk of gastrointestinal bleeding, such as histamine blockers or sucralfate
- Monitor complete blood counts and maintain hemoglobin concentrations within an optimal range
- Transfuse packed red blood cells in cases of severe anemia, and fresh frozen plasma or platelets in cases of disseminated intravascular coagulation (DIC).



### ***Corticosteroid and Immunotherapy***

- Consider corticosteroids like hydrocortisone in fluid-refractory and catecholamine-dependent septic shock, especially when adrenal insufficiency is suspected
- Although various agents like IVIg, ibuprofen, and TNF antibodies have been tried, their clinical efficacy remains unproven.

### ***Nutritional Support***

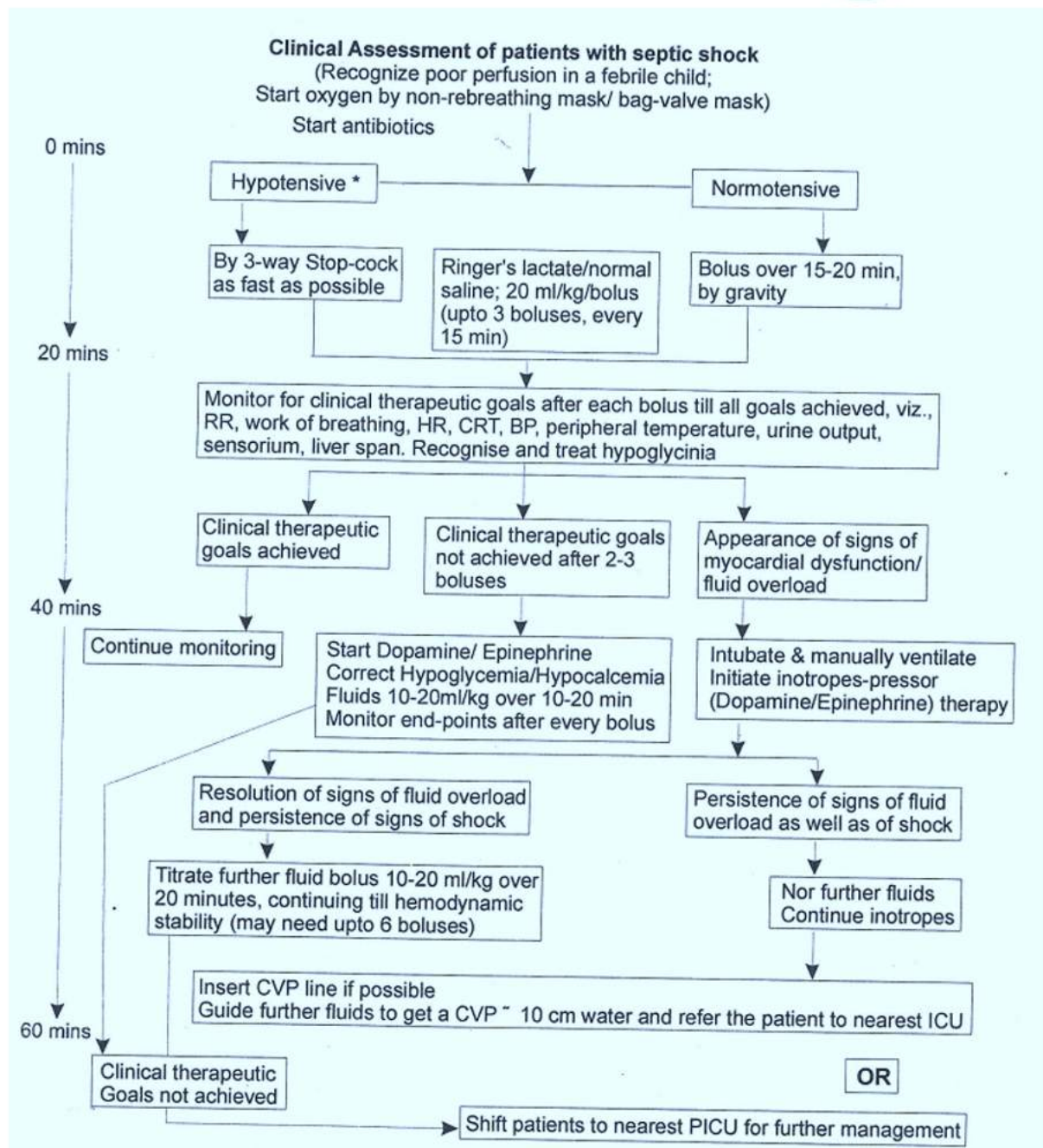
- Initiate nutritional support as early as possible, preferably through enteral routes, taking into account the patient's hemodynamic status and gastrointestinal function.

### ***Consultation, Transfer, and Family Support***

- Consult pediatric critical care specialists and consider transferring the patient to a facility with pediatric intensive care capabilities if not already in such a setting
- Maintain open and honest communication with the family, providing emotional support and involving them in decision-making processes.

### ***Extracorporeal Membrane Oxygenation (ECMO)***

- Consider as a last resort in cases of refractory shock or cardiac arrest, although its success is limited.



## 6. a) Outline the medical management of Patent Ductus Arteriosus (PDA).

- ❖ Patent ductus arteriosus (PDA) is a congenital heart condition where the ductus arteriosus, a fetal blood vessel connecting the pulmonary artery and the aorta, fails to close after birth.
- ❖ The medical management of PDA in neonates, infants, and children varies based on age, clinical presentation, and the response to treatment.



- ❖ Close monitoring, echocardiography, and collaboration with a pediatric cardiologist are essential components of care.
- ❖ In some cases, surgical or transcatheter interventions may be required to achieve closure and prevent complications associated with PDA.

### Neonates:

1. **Indomethacin or Ibuprofen:** In neonates, especially preterm infants, medical closure of PDA is often the first-line approach.
  - **Indomethacin:** Administered intravenously in three doses, usually 12-24 hours apart, it inhibits prostaglandin synthesis, which helps close the PDA.
  - **Ibuprofen:** Similar to indomethacin, ibuprofen is given in multiple doses and can be an alternative.
2. **Hemodynamic Monitoring:** Continuous monitoring of vital signs, echocardiography, and blood oxygen saturation is essential to assess the response to treatment.
3. **Fluid Management:** Adequate hydration is crucial to maintain renal perfusion while the PDA is closing. Intravenous fluids may need adjustment based on clinical status.
4. **Potential Side Effects:** Close monitoring for potential side effects of indomethacin or ibuprofen, such as gastrointestinal bleeding or renal dysfunction, is necessary.

### Infants:

1. **Indomethacin/Ibuprofen:** In full-term infants, especially those with significant hemodynamic compromise or failure to thrive, medical management with indomethacin or ibuprofen is considered.
2. **Echocardiographic Guidance:** Echocardiography is used to assess the size of the PDA, shunt severity, and the response to medical therapy.
3. **Fluid and Nutrition Management:** Adequate nutrition and hydration are essential for infants. In some cases, enteral feeding may be temporarily withheld during treatment.
4. **Follow-Up:** Close follow-up with a pediatric cardiologist is essential to monitor the progress and assess the need for additional courses of medication.

### Children:

1. **Prostaglandin Inhibitors:** In older children, medical management with indomethacin or ibuprofen is less effective due to the decreased sensitivity of the PDA to prostaglandin inhibition. However, it may still be attempted in specific cases.
2. **Echocardiographic Assessment:** Echocardiography helps determine the size and hemodynamic significance of the PDA. This information guides the management plan.
3. **Surgical Ligation:** If medical management is unsuccessful or contraindicated, surgical ligation is considered. This procedure involves closing the PDA through a small incision in the chest. It is typically performed under general anesthesia.
4. **Transcatheter Occlusion:** In some cases, particularly in older children and adolescents, transcatheter occlusion using specialized devices may be an alternative to surgery.
5. **Complications Management:** Management of complications related to PDA, such as infective endocarditis, congestive heart failure, or pulmonary hypertension, is essential.
6. **Regular Cardiology Follow-Up:** Children with PDA, whether managed medically or surgically, require regular follow-up with a pediatric cardiologist to monitor their heart function and growth.

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### 6. b) How will you differentiate an innocent murmur from an organic cardiac murmur?

- Differentiating between innocent and organic murmurs is a nuanced process that relies heavily on clinical acumen and appropriate use of diagnostic tools.
- It's crucial to approach each case individually, considering the patient's age, symptoms, and the murmur's characteristics.
- When in doubt, echocardiography remains the gold standard for evaluation.

#### Clinical considerations :

- **History and Physical Examination:** Emphasize the importance of a thorough history and physical examination. Pay attention to the murmur's characteristics and associated findings.
- **Age Considerations:** Remember that innocent murmurs are more common in children and young adults.



- **Use of Maneuvers:** Teach how to use positional changes and maneuvers to differentiate murmurs.
- **Referral for Imaging:** Stress the importance of echocardiography in any doubtful case or if there are any associated symptoms or signs suggesting organic heart disease.
- **Continual Reassessment:** Encourage regular follow-up and reassessment, as the clinical context may change over time.

### Characteristics of Innocent Murmurs:

1. **Sound Quality:**
  - Typically soft (intensity grade 1-2/6).
  - Musical or vibratory quality.
  - Best heard at the left lower sternal border or the pulmonary area.
2. **Variability with Position or Maneuvers:**
  - Changes or disappears with position (sitting, standing, supine).
  - May diminish or vanish with Valsalva maneuver.
3. **No Associated Cardiac Symptoms:**
  - Absence of symptoms like dyspnea, chest pain, syncope, or cyanosis.
4. **Normal Cardiac Examination:**
  - Normal S1 and S2, no extra heart sounds or clicks.
  - Absence of heave or thrill.
5. **Age and Growth Patterns:**
  - Common in children and adolescents; often associated with periods of rapid growth.
6. **No Radiation:**
  - Limited area of audibility, does not radiate widely.

### Characteristics of Organic Murmurs:

1. **Sound Quality:**
  - Often louder (grade 3/6 or higher).
  - Harsh, blowing, or rumbling quality.

- May be associated with a thrill.

## 2. **Consistency:**

- Less likely to change with position or maneuvers.

## 3. **Associated Cardiac Symptoms:**

- May present with symptoms of heart failure, cyanosis, or exercise intolerance.

## 4. **Abnormal Cardiac Examination:**

- Abnormal heart sounds (S3, S4, clicks).
- Evidence of cardiac enlargement or abnormal pulses.

## 5. **Radiation:**

- Often radiates to other areas (e.g., aortic stenosis murmur radiates to the neck).

## 6. **Persistence:**

- Does not resolve over time or with changes in growth.

## Diagnostic Tools:

### 1. **Echocardiography:**

- Essential for confirming the presence of structural heart disease.
- Provides detailed information about heart anatomy and function.

### 2. **Electrocardiogram (ECG):**

- Can show signs of chamber enlargement or strain patterns.

### 3. **Chest X-ray:**

- May show cardiac enlargement or pulmonary vascular changes.

### 4. **Cardiac MRI or CT:**

- In selected cases for detailed anatomical assessment.

| Characteristic | Innocent Murmur                          | Organic Murmur                                                  |
|----------------|------------------------------------------|-----------------------------------------------------------------|
| Sound Quality  | Soft (grade 1-2/6), musical or vibratory | Often louder (grade 3/6 or higher), harsh, blowing, or rumbling |



|                                            |                                                                         |                                                                                   |
|--------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <b>Variability with Position/Maneuvers</b> | Changes or disappears with position changes or Valsalva maneuver        | Consistent, less likely to change with position or maneuvers                      |
| <b>Associated Cardiac Symptoms</b>         | Absent (no dyspnea, chest pain, syncope, or cyanosis)                   | May present (heart failure symptoms, cyanosis, exercise intolerance)              |
| <b>Cardiac Examination</b>                 | Normal S1 and S2, no extra heart sounds or clicks, no thrill or heave   | Abnormal heart sounds (S3, S4, clicks), possible thrill or heave, abnormal pulses |
| <b>Age and Growth Patterns</b>             | Common in children and adolescents, often associated with growth spurts | Can occur at any age, not related to growth patterns                              |
| <b>Radiation</b>                           | Limited area of audibility, does not radiate widely                     | Often radiates to other areas (e.g., neck in aortic stenosis)                     |
| <b>Persistence</b>                         | Often resolves over time or with changes in growth                      | Persistent, does not resolve spontaneously                                        |
| <b>Diagnostic Tools</b>                    | Usually not required, echocardiography if in doubt                      | Echocardiography essential, may require ECG, chest X-ray, or advanced imaging     |

- **Echocardiography:** While often not necessary for innocent murmurs, it is the definitive tool for evaluating suspected organic murmurs.
- **Clinical Judgment:** The distinction between innocent and organic murmurs is not always clear-cut and requires careful clinical judgment.
- **Regular Monitoring:** Innocent murmurs should be monitored for changes that might suggest the development of an organic pathology.

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## 7. a) Describe the physiological basis of gastroesophageal reflux.

- Gastroesophageal reflux (GER) is a common physiological phenomenon in infants and children, characterized by the passage of gastric contents into the esophagus
- GER in infants and children is multifactorial, involving anatomical, physiological, neurodevelopmental, and behavioral components
- The immaturity of the LES and the gastrointestinal tract plays a central role

- Most infants experience some degree of GER, which is generally benign and self-limiting, resolving as the child grows and the gastrointestinal system matures
- However, when GER leads to symptoms or complications, it is termed gastroesophageal reflux disease (GERD), warranting further evaluation and management.
- The physiological basis of GER involves several factors:

### Lower Esophageal Sphincter (LES) Function:

#### 1. *Tone and Maturity:*

- In infants, the LES may have lower baseline tone compared to older children and adults.
- This reduced tone allows easier passage of stomach contents back into the esophagus.

#### 2. *Transient Relaxations:*

- Transient Lower Esophageal Sphincter Relaxations (TLESRs) are the primary mechanism of GER in both children and adults.
- These are periods when the LES relaxes independently of swallowing, allowing reflux.

#### 3. *Developmental Maturation:*

- The LES tone and control mature over time, which is why GER is more common in infants and tends to improve with age.

### Gastric Factors:

#### 1. *Gastric Emptying:*

- Delayed gastric emptying can contribute to GER, as it leads to increased gastric volume and pressure.
- In some children, gastric emptying is slower, exacerbating reflux.

#### 2. *Gastric Composition:*

- The composition of gastric contents, including acid and pepsin, can affect the severity of reflux symptoms and mucosal injury.

### Anatomical Considerations:

#### 1. *Angle of His:*



- The angle between the esophagus and the stomach (Angle of His) in infants is more acute, which may provide less of an anatomical barrier to reflux.

## 2. **Esophageal Length:**

- Shorter esophageal length in infants means the distance between the stomach and the pharynx is reduced, facilitating reflux.

## 3. **Hiatal Hernia:**

- Although less common in children, a hiatal hernia can disrupt normal LES function and contribute to GER.

## Neurodevelopmental Factors:

### 1. **Neurological Control:**

- Immature neurological control of the gastrointestinal tract in infants can contribute to the frequency and duration of TLESRs.

### 2. **Coordination of Swallowing and Esophageal Peristalsis:**

- Inefficient coordination between swallowing and esophageal motility can lead to increased reflux episodes.

## Dietary and Behavioral Factors:

### 1. **Feeding Practices:**

- Overfeeding, rapid feeding, and the use of certain formulas can increase the likelihood of GER.
- Positioning during and after feeding also plays a role.

### 2. **Diet and Food Sensitivities:**

- Certain foods and feeding practices can exacerbate GER symptoms.

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## 7. b) Discuss clinical features and management of GERD.

- ❖ GERD in infants and children is a complex condition with a spectrum of presentations.
- ❖ A thorough understanding of its clinical features, coupled with a judicious approach to diagnosis and management, is essential.

- ❖ The goal is to alleviate symptoms, promote normal growth and development, and prevent complications.
- ❖ Regular follow-up and adjustment of management plans are crucial to achieving these objectives.

### **Clinical Features of GERD:**

#### **1. Age-Dependent Symptoms:**

- **Infants:** Regurgitation, vomiting, irritability, feeding refusal, failure to thrive, arching of the back during feeds.
- **Older Children:** Heartburn, abdominal pain, non-cardiac chest pain, chronic cough, hoarseness, asthma-like symptoms.

#### **2. Atypical Presentations:**

- Dental erosions, sinusitis, otitis media, recurrent pneumonia.
- In severe cases, esophagitis, anemia, or hematemesis.

#### **3. Differentiation from Physiological GER:**

- GERD is distinguished from normal GER by the frequency and severity of symptoms and the presence of complications like esophagitis, systemic manifestations like aspiration pneumonitis or poor weight gain/ failure to thrive.

### **Diagnostic Approach:**

#### **1. Clinical History and Physical Examination:**

- Detailed feeding and symptom history.
- Growth chart review for failure to thrive.
- Physical examination to rule out other causes of symptoms.

#### **2. Diagnostic Testing:**

- **Upper Gastrointestinal Series:** Useful for ruling out anatomical abnormalities but not for diagnosing GERD.
- **Esophagogastroduodenoscopy (EGD) with Biopsy:** Gold standard for diagnosing esophagitis.
- **pH Monitoring or pH-Impedance Monitoring:** To quantify acid reflux and correlate symptoms with reflux episodes.



- **Empirical Trial of Acid Suppression:** Can be diagnostic and therapeutic.

### **Management of GERD:**

#### **1. Lifestyle and Dietary Modifications:**

- **Infants:** Smaller, more frequent feedings; thickening of feeds; positioning therapy (keeping upright after feeding).
- **Older Children:** Avoidance of caffeine, chocolate, spicy foods, and late meals; weight management.

#### **2. Pharmacological Therapy:**

- **Proton Pump Inhibitors (PPIs):** First-line therapy for esophagitis and severe GERD.
- **Histamine-2 Receptor Antagonists (H2RAs):** Alternative to PPIs, though less effective for esophagitis.
- **Prokinetic Agents:** Limited role due to side effect profiles.

#### **3. Surgical Intervention:**

- Considered in refractory cases or when complications like Barrett's esophagus develop.
- Nissen fundoplication is the most common procedure.

#### **4. Monitoring and Follow-Up:**

- Regular follow-up to monitor growth, development, and symptom resolution.
- Gradual weaning of medications as symptoms improve.

#### **5. Complications:**

- Esophagitis, esophageal strictures, Barrett's esophagus, respiratory complications.

### **Imp. Practical Points:**

- Differentiate and discriminate GER from GERD; for GER just reassurance is needed
- **Holistic Approach:** Emphasize the importance of a comprehensive approach, including history, physical examination, and selective use of diagnostic tests.
- **Individualized Treatment:** Tailor management strategies to individual patient needs, considering age, symptom severity, and response to therapy.

- **Evidence-Based Medicine:** Encourage familiarity with the latest guidelines and evidence for managing GERD in pediatric populations.
- **Multidisciplinary Collaboration:** Highlight the role of collaboration with dietitians, pediatricians, and surgeons in complex cases.

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### 8. a) Recent advances in insulin therapy.

- ❖ Recent advances in insulin therapy reflect a continuous effort to improve diabetes management, particularly focusing on enhancing glycemic control, reducing hypoglycemia risk, and improving patient quality of life
- ❖ The landscape of insulin therapy is rapidly evolving, with advancements aimed at improving the ease of use, reducing the burden of disease management, and minimizing the risk of complications
- ❖ These innovations represent a significant step forward in personalized diabetes care, offering more options tailored to individual patient needs and lifestyles
- ❖ However, access to these advanced therapies can be limited by cost and healthcare infrastructure, highlighting the need for continued efforts in making diabetes care more accessible and equitable globally.

#### 1. Fast-Acting Insulin Analogues

- **Fiasp (Faster-Acting Insulin Aspart):**
  - Contains niacinamide for faster absorption.
  - Begins working in about 2.5 minutes, ideal for post-meal glucose spikes.
- **Lyumjev (Ultra Rapid Lispro):**
  - Rapid onset of action, mimicking natural insulin response more closely.
  - Reduces postprandial glucose excursions.

#### 2. Ultra-Long-Acting Insulin Analogues

- **Tresiba (Insulin Degludec):**
  - Ultra-long duration of action (up to 42 hours), allowing for flexibility in dosing time.
  - Lower risk of nocturnal hypoglycemia.



- ***Toujeo (Insulin Glargine U300):***

- Three times the concentration of standard insulin glargine.
- Provides a more stable and prolonged glycemic control.

### 3. Insulin Pumps and Continuous Glucose Monitoring (CGM) Integration

- ***Closed-Loop Systems (Artificial Pancreas):***

- Combines insulin pump with CGM.
- Automatically adjusts insulin delivery based on real-time glucose readings.

- ***Hybrid Closed-Loop Systems:***

- Medtronic's MiniMed 670G and 770G.
- Tandem's t:slim X2 with Control-IQ technology.

### 4. Inhaled Insulin

- ***Afrezza:***

- Rapid-acting inhaled insulin.
- Convenient for patients averse to injections.
- Quick onset and short duration, mimicking prandial insulin spikes.

### 5. Smart Insulin Pens

- ***InPen and NovoPen 6:***

- Bluetooth-enabled pens that track dosing and timing.
- Integrate with smartphone apps for dose reminders and glucose monitoring.

### 6. Concentrated Insulins

- ***U-500 Regular Insulin:***

- For insulin-resistant patients requiring high doses.
- Reduces the volume of injections.

### 7. Biosimilar Insulins

- ***Basaglar (Biosimilar to Lantus):***

- Offers a lower-cost alternative to insulin glargine.

- Similar efficacy and safety profile.

## 8. Oral Insulin

- **Ongoing Research:**

- Developing insulin that can be taken orally.
- Challenges include insulin degradation in the stomach and absorption issues.

## 9. Glucose-Responsive Insulin

- **Smart Insulin:**

- Still in research phase.
- Designed to activate in response to hyperglycemia and deactivate when normal glucose levels are reached.

## 10. Gene Therapy

- **Potential Future Development:**

- Gene editing to restore insulin production in pancreatic beta cells.
- Still in early research stages.

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### 8. b) Clinical features of classical CAH.

- ❖ Classical congenital adrenal hyperplasia (CAH), most commonly due to 21-hydroxylase deficiency, presents with a spectrum of clinical features that can vary based on the severity of the enzyme deficiency
- ❖ The condition is characterized by impaired cortisol and often aldosterone synthesis, with an excess of androgenic precursors
- ❖ Classical CAH presents a range of clinical features that are primarily driven by androgen excess and, in many cases, cortisol and aldosterone deficiencies
- ❖ The presentation can vary significantly between individuals and requires a high index of suspicion, especially in newborns with ambiguous genitalia or those who develop a salt-wasting crisis
- ❖ Early diagnosis and appropriate hormonal replacement therapy are crucial for preventing adrenal crises and managing the long-term consequences of the disease.



### In Newborn Females (With Salt-Wasting and Simple Virilizing Forms):

#### 1. **Virilization of External Genitalia:**

- Ambiguous genitalia at birth, such as clitoromegaly, labial fusion, and a urogenital sinus.
- Internal reproductive organs (uterus, fallopian tubes, ovaries) are typically normal.

#### 2. **Salt-Wasting Crisis:**

- Occurs in about 75% of cases with classical CAH.
- Presents within the first few weeks of life.
- Symptoms include vomiting, dehydration, hypotension, hyponatremia, hyperkalemia, and shock.

### In Newborn Males (With Salt-Wasting Form):

#### 1. **Normal Male Genitalia:**

- Often diagnosed later than females due to lack of genital ambiguity.
- May have subtle signs like hyperpigmentation.

#### 2. **Salt-Wasting Crisis:**

- Similar presentation as in females, often leading to the diagnosis.

### In Both Genders (With Simple Virilizing Form, Without Salt-Wasting):

#### 1. **Rapid Growth and Precocious Puberty:**

- Accelerated growth velocity and skeletal maturation.
- Early development of secondary sexual characteristics.

#### 2. **Advanced Bone Age:**

- Can lead to early epiphyseal closure and short adult stature.

#### 3. **Androgen Excess:**

- Severe acne, hirsutism, and male-pattern baldness in adolescence.

### In Both Genders (With Salt-Wasting and Simple Virilizing Forms):

#### 1. **Hyperpigmentation:**

- Due to excess ACTH stimulating melanocytes.
- More pronounced in skin creases, nipples, and genitalia.

## 2. **Adrenal Crisis:**

- Risk of life-threatening adrenal crisis due to cortisol deficiency, especially during stress or illness.

### Diagnostic Features:

#### 1. **Elevated 17-Hydroxyprogesterone Levels:**

- Diagnostic hallmark of 21-hydroxylase deficiency CAH.

#### 2. **Electrolyte Imbalances:**

- In salt-wasting form, hyponatremia and hyperkalemia.

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## 9. a) Discuss the differential diagnosis in a 6-year-old child with easy bruisability.

- ❖ Easy bruisability in a 6-year-old child can be a sign of various underlying conditions, ranging from benign to serious
- ❖ When evaluating a child with this symptom, it's important to consider a broad differential diagnosis
- ❖ The differential diagnosis for easy bruisability in a child is extensive and requires a systematic approach to evaluation
- ❖ While benign causes are common, it is crucial to rule out serious conditions such as hematological disorders and non-accidental injury
- ❖ A thorough history, physical examination, and appropriate laboratory investigations are key to arriving at an accurate diagnosis and guiding management.

### Hematological Causes:

#### 1. **Platelet Disorders:**

- **Idiopathic Thrombocytopenic Purpura (ITP):** Autoimmune destruction of platelets.
- **Thrombocytopenia:** Due to bone marrow suppression or infiltration (leukemia, aplastic anemia).
- **Congenital Platelet Function Disorders:** Such as Glanzmann thrombasthenia.

#### 2. **Coagulation Disorders:**



- **Hemophilia:** X-linked recessive disorder affecting clotting factors VIII (Hemophilia A) or IX (Hemophilia B).
- **Von Willebrand Disease:** Affects platelet function and blood clotting.
- **Vitamin K Deficiency:** Can affect coagulation factor synthesis.

### 3. Bone Marrow Disorders:

- **Leukemia:** Particularly acute lymphoblastic leukemia, common in this age group.
- **Aplastic Anemia:** Pancytopenia including thrombocytopenia.

## Non-Hematological Causes:

### 1. Vascular Disorders:

- **Henoch-Schönlein Purpura (HSP):** Vasculitis causing purpura, abdominal pain, arthritis, and renal involvement.
- **Ehlers-Danlos Syndrome:** Connective tissue disorder causing fragile blood vessels.

### 2. Infections:

- Certain infections can cause thrombocytopenia or vasculitis, leading to increased bruising.

### 3. Nutritional Deficiencies:

- **Vitamin C Deficiency (Scurvy):** Affects collagen synthesis and blood vessel integrity.

### 4. Physical Causes:

- **Non-accidental Injury (Child Abuse):** Must always be considered in unexplained bruising.
- **Accidental Bruising:** Common in active children, but the pattern and location can usually differentiate from pathological causes.

## Other Considerations:

### 1. Medications:

- Some medications, including anticoagulants and nonsteroidal anti-inflammatory drugs (NSAIDs), can increase bruising risk.

### 2. Liver Disease:

- Can affect coagulation factor synthesis.

### 3. *Systemic Illnesses:*

- Conditions like systemic lupus erythematosus (SLE) can have hematological manifestations.

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## 9. b) Enumerate relevant investigation for each differential diagnosis.

### Diagnostic Approach:

#### 1. *Detailed History:*

- Assess for family history of bleeding disorders, medication use, dietary history, and any signs of systemic illness.

#### 2. *Physical Examination:*

- Look for patterns of bruising, signs of vasculitis, joint hypermobility, or other systemic findings.

#### 3. *Laboratory Tests:*

- Complete blood count (CBC) with platelet count.
- Coagulation profile (PT, aPTT, INR).
- Bone marrow examination if indicated.
- Specific tests based on suspected diagnosis (e.g., factor VIII and IX levels for hemophilia).

| <b>Differential Diagnosis</b>                    | <b>Key Features</b>                                                          | <b>Diagnostic Approach</b>                                              | <b>Management</b>                                                             |
|--------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| <b>Idiopathic Thrombocytopenic Purpura (ITP)</b> | Sudden onset of bruising, petechiae; often history of recent viral infection | CBC with platelet count; bone marrow aspiration if uncertain            | Observation or corticosteroids; IVIG or anti-D immunoglobulin in severe cases |
| <b>Hemophilia (A or B)</b>                       | Family history (X-linked); large, deep bruises; hemarthrosis                 | Factor VIII/IX assay; aPTT prolonged                                    | Factor replacement therapy; desmopressin (DDAVP) in mild Hemophilia A         |
| <b>Von Willebrand Disease</b>                    | Mucosal bleeding, family history of bleeding disorder                        | Von Willebrand factor assay, factor VIII level, platelet function tests | Desmopressin, Von Willebrand factor-containing products                       |



|                                            |                                                                      |                                                                    |                                                                 |
|--------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Leukemia</b>                            | Fatigue, fever, bone pain, pallor, lymphadenopathy                   | CBC with differential, bone marrow biopsy, imaging studies         | Chemotherapy, supportive care, potential bone marrow transplant |
| <b>Aplastic Anemia</b>                     | Pancytopenia, recurrent infections, fatigue                          | CBC, bone marrow biopsy                                            | Immunosuppressive therapy, bone marrow transplant               |
| <b>Vitamin K Deficiency</b>                | Bleeding gums, epistaxis, GI bleeding                                | PT/INR, vitamin K level                                            | Vitamin K supplementation                                       |
| <b>Henoch-Schönlein Purpura (HSP)</b>      | Palpable purpura, abdominal pain, arthritis, renal involvement       | Clinical diagnosis, urinalysis, renal function tests               | Supportive care, corticosteroids for severe cases               |
| <b>Ehlers-Danlos Syndrome</b>              | Joint hypermobility, skin hyperelasticity, family history            | Clinical diagnosis, genetic testing                                | Supportive care, physical therapy, avoidance of trauma          |
| <b>Scurvy (Vitamin C Deficiency)</b>       | Perifollicular hemorrhages, swollen gums, corkscrew hairs            | Dietary history, vitamin C level                                   | Vitamin C supplementation                                       |
| <b>Non-accidental Injury (Child Abuse)</b> | Inconsistent history, patterned bruising, multiple stages of healing | Multidisciplinary evaluation, skeletal survey, ophthalmologic exam | Child protection involvement, supportive care                   |
| <b>Liver Disease</b>                       | Jaundice, hepatomegaly, ascites                                      | Liver function tests, ultrasound                                   | Treat underlying cause, vitamin K supplementation               |
| <b>Systemic Lupus Erythematosus (SLE)</b>  | Rash, joint pain, systemic symptoms                                  | ANA, anti-dsDNA, complement levels                                 | Corticosteroids, immunosuppressants                             |

- **Individualized Management:** Management strategies should be tailored to the specific diagnosis and severity of the condition.
- **Multidisciplinary Approach:** In many cases, especially in complex disorders like leukemia or SLE, a team approach involving various specialties is essential.
- **Monitoring and Follow-Up:** Regular monitoring is crucial, particularly in chronic conditions like ITP or hemophilia, to assess treatment efficacy and adjust therapy as needed.
- **Preventive Measures:** In conditions like hemophilia and Ehlers-Danlos syndrome, preventive measures to avoid trauma and bleeding are important.

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### 10. a) Outline management of dog bite in a 4-year-old child.

According to the World Health Organization (WHO), the management of a dog bite depends on various factors such as the location of the bite, the overall health condition of the bitten person, and the vaccination status of the dog.

#### Dog Bite Management Based on Severity

##### Minor Wounds

- **Immediate Care:** Wash the wound with soap and water for at least five minutes.
- **Antiseptic:** Apply an antiseptic solution.
- **Tetanus Prophylaxis:** Update tetanus vaccination if needed.
- **Antibiotics:** Not usually required unless there are signs of infection.

##### Moderate to Severe Wounds

- **Immediate Care:** Immediate medical attention is required.
- **Wound Culture:** May be necessary to determine the appropriate antibiotic.
- **Antibiotics:** Broad-spectrum antibiotics are usually prescribed.
- **Surgical Intervention:** May be required for deep wounds, especially those affecting muscles, tendons, or bones.

##### Unknown or Unvaccinated Dog

- **Rabies Prophylaxis:** Post-exposure prophylaxis (PEP) for rabies may be required.

##### Vaccinated Dog

- **Rabies Prophylaxis:** Usually not required if the dog is up-to-date on vaccinations.

***In either case 10 days observation for dog***

#### Dos and Don'ts in Case of a Dog Bite (Patient education )

##### Dos

- Wash the wound immediately with soap and water.
- Seek medical attention for moderate to severe wounds.
- Report the incident to local health authorities.

##### Don'ts



- Do not ignore even minor wounds, especially if inflicted by an unknown or unvaccinated dog.
- Do not apply any traditional remedies to the wound.
- Do not suture the wounds

#### WHO Categories of Exposure and Recommended PEP

- **Category I (Touching or feeding animals, licks on intact skin):** No PEP required.
- **Category II (Nibbling of uncovered skin, minor scratches without bleeding):** Immediate vaccination.
- **Category III (Single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membrane with saliva from licks):** Immediate vaccination and administer Rabies Immunoglobulin.

#### Active Immunization: Rabies Vaccine

The rabies vaccine is administered intramuscularly and is the cornerstone of rabies Post-Exposure Prophylaxis (PEP). The WHO recommends a variety of regimens based on the site of the bite and the grade of injury.

##### Intramuscular (IM) Regimens

1. **Essen Regimen:** 5 doses on days 0, 3, 7, 14, and 28.
2. **Zagreb Regimen:** 2 doses on day 0, then single doses on days 7 and 21.

##### Intradermal (ID) Regimens

1. **Updated Thai Regimen:** 2-site ID on days 0, 3, and 7, then a booster at 1 year.

#### Passive Immunization: Rabies Immunoglobulin (RIG)

Rabies immunoglobulin provides immediate antibodies until the body can respond to the vaccine by actively producing its own antibodies. RIG is indicated for severe bites (WHO category III), and it should be infiltrated around the wound.

##### Human Rabies Immunoglobulin (HRIG)

- Dose: 20 IU/kg body weight
- Infiltrate as much as possible around the wound.

##### Equine Rabies Immunoglobulin (ERIG)

- Dose: 40 IU/kg body weight

- Infiltrate as much as possible around the wound.

#### Note

- Rabies immunoglobulin is not recommended for category I and II exposures.
- Rabies immunoglobulin is recommended as soon as possible for category III exposures, and it can be administered up to the 7th day after the first dose of the rabies vaccine

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### 10. b) Describe management of scorpion bite.

#### Pathogenesis

- **Venom Composition:** Scorpion venom contains a complex mixture of neurotoxins, enzymes, and other substances.
- **Neurotoxic Effects:** The venom primarily affects the nervous system, leading to the release of neurotransmitters like acetylcholine and catecholamines.
- **Systemic Effects:** These neurotransmitters can cause a range of systemic effects including hypertension, tachycardia, and sometimes even multi-organ failure.

#### Clinical Features

- **Local Symptoms:** Pain, swelling, and redness at the sting site.
- **Neurological Symptoms:** Restlessness, hyperactivity, muscle twitching, and in severe cases, convulsions.
- **Cardiovascular Symptoms:** Tachycardia, hypertension, and in severe cases, heart failure.
- **Respiratory Symptoms:** Shortness of breath, respiratory distress, and in severe cases, pulmonary edema.
- **Gastrointestinal Symptoms:** Nausea, vomiting, and abdominal pain.
  - IV fluids for hydration.
  - Oxygen therapy for respiratory distress.

#### Monitoring

- **Cardiac Monitoring:** Continuous ECG monitoring for cardiovascular symptoms.
- **Vital Signs:** Regular monitoring of blood pressure, heart rate, and respiratory rate.



### Follow-up

- **Outpatient Care:** For mild cases with local symptoms only.
- **Hospital Admission:** For moderate to severe cases with systemic symptoms.

### Note

- The severity of symptoms and the necessity for antivenom administration are determined by the clinical presentation.
- Early medical intervention improves the prognosis significantly.

## Management of Scorpion Sting

### Immediate First Aid

- **Local Care:** Wash the sting area with soap and water, and apply a cold compress.
- **Immobilization:** Keep the affected limb immobilized at heart level.

### Medical Treatment

#### Analgesia

- **Paracetamol:**
  - **Mode of Action:** Inhibits COX enzymes, reducing prostaglandin synthesis.
  - **Dose:** 10-15 mg/kg every 4-6 hours.
  - **Side Effects:** Hepatotoxicity in overdose.
- **Opioids (Morphine):**
  - **Mode of Action:** Binds to opioid receptors, blocking pain signals.
  - **Dose:** 0.1-0.2 mg/kg IV.
  - **Side Effects:** Respiratory depression, constipation, addiction potential.

#### Antivenom

- **Scorpion Antivenom:**
  - **Mode of Action:** Neutralizes the venom's toxic effects.
  - **Dose:** Varies depending on severity; consult manufacturer's guidelines.
  - **Side Effects:** Anaphylaxis, serum sickness.

### Symptomatic Treatment

- **Antihistamines (Diphenhydramine):**
  - **Mode of Action:** Blocks H1 receptors, reducing allergic symptoms.
  - **Dose:** 1-2 mg/kg IV.
  - **Side Effects:** Sedation, dry mouth.
- **Benzodiazepines (Diazepam):**
  - **Mode of Action:** Enhances GABA activity, reducing CNS excitability.
  - **Dose:** 0.1-0.3 mg/kg IV.
  - **Side Effects:** Respiratory depression, sedation.
- **Antihypertensives (Labetalol):**
  - **Mode of Action:** Alpha and beta-blocker, reducing BP and heart rate.
  - **Dose:** 0.2-1 mg/kg IV.
  - **Side Effects:** Hypotension, bradycardia.

## Prazosin

### Mode of Action

- **Alpha-1 Adrenergic Receptor Blocker:** Prazosin primarily blocks alpha-1 adrenergic receptors, leading to vasodilation and a decrease in systemic vascular resistance, which can counteract the hypertension and myocardial dysfunction caused by scorpion venom.

### Dose

- **Initial Dose:** 250 mcg to 500 mcg in children, titrated up based on response.
- **Maintenance Dose:** 500 mcg to 1 mg every 6 hours, adjusted according to clinical response.

### Side Effects

- **Hypotension:** Particularly postural hypotension.
- **Dizziness or Fainting:** Especially upon standing up.
- **Nausea:** Less commonly.

### Indications in Scorpion Sting

- **Hypertension:** To control elevated blood pressure.



- **Pulmonary Edema:** To reduce preload and afterload, aiding in the management of pulmonary edema.

## Phenoxybenzamine

### Mode of Action

- **Non-selective Alpha Blocker:** Phenoxybenzamine blocks both alpha-1 and alpha-2 adrenergic receptors, causing vasodilation.
- **Irreversible Binding:** Unlike prazosin, the binding is irreversible, leading to a more prolonged effect.

### Dose

- **Initial Dose:** 0.2 mg/kg in children, up to a maximum of 10 mg.
- **Maintenance Dose:** 0.2 to 0.4 mg/kg every 6 to 12 hours.

### Side Effects

- **Hypotension:** Can be more severe than with prazosin due to irreversible binding.
- **Tachycardia:** As a compensatory response to hypotension.
- **Dry Mouth and Fatigue:** Less commonly.

### Indications in Scorpion Sting

- **Severe Cardiovascular Manifestations:** Used in severe cases involving hypertension and myocardial dysfunction.
- **Not First-Line:** Generally reserved for cases where other treatments have failed due to its irreversible action and side effect profile.

## Supportive Care

- **IV Fluids:** ½ Normal saline or lactated Ringer's for hydration.
- **Oxygen Therapy:** For patients with respiratory distress; titrate to maintain SpO<sub>2</sub> > 94%.

### Monitoring

- **Cardiac Monitoring:** Continuous ECG.
- **Vital Signs:** Regular monitoring of BP, heart rate, and respiratory rate.

### Follow-up

- **Outpatient Care:** For mild cases.

- **Hospital Admission:** For moderate to severe cases.

## Paper 4

### 1. a) How will you manage a 2-year-old child presenting with status epilepticus?

#### **Definition of Status Epilepticus**

- **Traditional Definition:** A seizure lasting more than 30 minutes or recurrent seizures without regaining consciousness between episodes.
- **Modern Definition:** A seizure lasting more than 5 minutes or two or more seizures within a 5-minute period without the person returning to normal between them.

#### **Causes:**

|                                                   |                                                                                                                                                                     |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fever.                                            |                                                                                                                                                                     |
| Intracranial infections                           | <ul style="list-style-type: none"> <li>- Meningitis.</li> <li>- Meningoencephalitis.</li> <li>- Brain Abscess.</li> </ul>                                           |
| Hypoxic Encephalopathy.                           |                                                                                                                                                                     |
| Cerebrovascular diseases.                         |                                                                                                                                                                     |
| Metabolic derangements                            | <ul style="list-style-type: none"> <li>- Hypoglycemia</li> <li>- Hyponatremia</li> <li>- Hypernatremia</li> <li>- Hypocalcemia</li> <li>- Hypomagnesemia</li> </ul> |
| Cerebral Tumors                                   | <ul style="list-style-type: none"> <li>- Benign.</li> <li>- Malignant-Primary, - Secondary</li> </ul>                                                               |
| Poisonings                                        |                                                                                                                                                                     |
| Congenital abnormalities of brain                 |                                                                                                                                                                     |
| Inborn errors of Metabolism.                      |                                                                                                                                                                     |
| Medications e.g.                                  | <ul style="list-style-type: none"> <li>- Theophylline</li> <li>- Tricyclic antidepressants</li> </ul>                                                               |
| Drug abuse e.g.                                   | <ul style="list-style-type: none"> <li>- Cocaine or other stimulants</li> </ul>                                                                                     |
| Epilepsy (First presentation of primary epilepsy) |                                                                                                                                                                     |

#### **Pathophysiological changes:**



| Compensation (< 30 minutes)                                                                                                                                                                                          | Decompensation (> 30 minutes)                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Increased cardiac output<br>Increased cerebral blood flow<br>Increased catecholamine release<br>Increased glucose concentration in the brain<br>Cerebral energy requirements matched by supply of oxygen and glucose | Failure of cerebral autoregulation<br>Hypoglycemia<br>Hypoxia<br>Acidosis<br>Hyponatremia, Hypo/hyperkalemia<br>Disseminated intravascular coagulation<br>Leucocytosis<br>Falling blood pressure and cardiac output<br>Rhabdomyolysis and renal failure |

### Approach to Status Epilepticus

#### Initial Assessment

- **Airway, Breathing, Circulation (ABCs):** Immediate stabilization.
- **Blood Work:** CBC, electrolytes, glucose, liver and renal function tests.
- **Imaging:** CT or MRI if new onset or focal features.
- **Lumbar Puncture:** If suspecting CNS infection.

#### Diagnostic Evaluation

- **EEG:** To confirm diagnosis and guide treatment.
- **Blood and Urine Tests:** To identify potential metabolic or toxic causes.
- **LP, Imaging:** If initial treatment is unsuccessful.

### Treatment of Status Epilepticus

#### Immediate Management

- **Benzodiazepines:** First-line treatment usually involves IV lorazepam or diazepam.
  - **Dosage:** Lorazepam 0.1 mg/kg IV, Diazepam 0.15-0.2 mg/kg IV.
  - **Efficacy:** Effective in terminating seizures in approximately 60-80% of cases.
  - **Side Effects:** Respiratory depression, hypotension.

#### Second-Line Agents

- **Phenytoin or Fosphenytoin:** If benzodiazepines are ineffective.
  - **Dosage:** Phenytoin 20 mg/kg IV, Fosphenytoin 20 mg PE/kg IV.
  - **Efficacy:** Additional 50% seizure control.
  - **Side Effects:** Cardiac arrhythmias, hypotension.

#### Third-Line Agents

- **Barbiturates or Propofol:** For refractory status epilepticus.
  - **Dosage:** Phenobarbital 20 mg/kg IV, Propofol 2 mg/kg IV followed by infusion.
  - **Efficacy:** Effective but with significant risk of respiratory depression.
  - **Side Effects:** Hypotension, respiratory depression.

#### Supportive Care

- **Fluids and Electrolytes:** Management of metabolic derangements.
- **Antipyretics:** For associated fever.
- **Antibiotics:** If bacterial infection is suspected.

#### Monitoring

- **Continuous EEG:** For seizure activity.
- **Vital Signs:** Continuous monitoring.
- **Blood Tests:** For drug levels and metabolic status.

#### Long-Term Management

- **Oral Antiepileptics:** Conversion to long-term seizure control medications.
- **Rehabilitation:** Physical and occupational therapy as needed.

#### Prognosis

- **Variable:** Depending on the underlying cause.
- **Mortality:** Ranges from 3-22%.

#### Special Considerations in Pediatrics

- **Dosing:** Weight-based dosing for all medications.
- **Monitoring:** More frequent monitoring due to variable pharmacokinetics.



***Complications of status epilepticus:***

|                       |                                                                                                                      |
|-----------------------|----------------------------------------------------------------------------------------------------------------------|
| <b>Cardiovascular</b> | Bradycardia, arrhythmia, cardiac failure or arrest, hypertension, hypotension, shock                                 |
| <b>Respiratory</b>    | Hyperapnea, apnea, irregular or cheyne stokes breathing, respiratory acidosis, aspiration pneumonia, pulmonary edema |
| <b>Renal</b>          | Oliguria, acute renal failure, acute tubular necrosis, myoglobinuria(from rhabdomyolysis)                            |
| <b>Autonomic</b>      | Hyperpyrexia, excessive sweating, excessive secretions with airway obstruction                                       |
| <b>Metabolic</b>      | Hyperglycemia, hypoglycemia, hyperkalemia, hyponatraemia, metabolic and lactic acidosis                              |



***Timeline in ER for managing case of status epilepticus***

| Time (min) | Drug treatment                                                                                                                                                                                          | Supportive treatment                                                                                                                                                                                                                                                                                    |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 0          |                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>Start O<sub>2</sub> and Ensure adequate respiration</li> <li>Considered Intubation</li> </ul>                                                                                                                                                                    |
| 2-3        |                                                                                                                                                                                                         | <ul style="list-style-type: none"> <li>Start an intravenous line with normal saline</li> <li>Draw blood for glucose, hepatic and renal function, CBC with DLC, electrolytes, calcium, magnesium, blood gases and toxicology screen (if indicated)</li> <li>Obtain urine for routine dipstick</li> </ul> |
| 3-5        | Diazepam: 0.3mg/kg or Lorazepam 0.1mg/kg-infused over 2 minutes                                                                                                                                         | <ul style="list-style-type: none"> <li>Start second I.V. line with normal saline for simultaneous administration of a second medication and I.V. fluids.</li> </ul>                                                                                                                                     |
| 7-8        | Phenytoin- 20mg/kg dilute in saline and infuse at a rate of no more than 1 mg/kg/min                                                                                                                    | <ul style="list-style-type: none"> <li>D25W- 2ml/kg I.V. push; Thiamine-100mg-I.V. push, Pyridoxine-100-200mg of I.V. push in children &lt; 18 months of age.</li> <li>Monitor blood pressure</li> </ul>                                                                                                |
| 10         | Repeat Diazepam/ Lorazepam                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                         |
| 15         | Repeat Diazepam/ Lorazepam                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                         |
| 20         | IV Valproate 30 mg/kg, if seizure controlled 5 mg/kg/hour for 6 hours* OR                                                                                                                               | Transfer to PICU, prepare for intubation, ventilation, get EEG.                                                                                                                                                                                                                                         |
| 20         | Diazepam or Midazolam infusion (Diazepam: 0.01mg/kg/min, max 0.1mg/kg/min, Midazolam: 2µg/kg/min up to 12 µg/kg/min in increments of 2µg/kg/min every 5 minutes (till seizure control)                  | Cardio respiratory monitoring                                                                                                                                                                                                                                                                           |
| 60         | Thiopental- load with 3-4 mg/kg and give over 2 minutes followed by an infusion at 0.2 mg/kg/min.increase the dose every 3-5minutes by 0.1mg/kg/min (until seizure control and the EEG is isoelectric.) | Start mechanical ventilation.                                                                                                                                                                                                                                                                           |

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## 1. b) Newer drugs in spinal muscular atrophy.

### Pharmacological Therapies

#### Nusinersen (Spinraza)

- **Drug Class:** Antisense oligonucleotide
- **Mechanism of Action:** Modifies pre-mRNA splicing of the SMN2 gene to increase production of functional SMN protein
- **FDA Approval:** December 2016
- **Indication:** Treatment of spinal muscular atrophy (SMA)

### Pharmacokinetics

- **Route of Administration:** Intrathecal
- **Distribution:** Central nervous system
- **Metabolism:** Nuclease degradation
- **Elimination:** Renal excretion

### Efficacy

- **Clinical Trials:** ENDEAR, CHERISH, NURTURE
- **Outcome Measures:** Hammersmith Functional Motor Scale Expanded (HFMSE), CHOP INTEND for infants
- **Results:** Significant improvement in motor function and survival rates in SMA

### Dosage

- **Loading Dose:** 12 mg per dose for the first three doses, with 14-day intervals; a fourth dose after 30 days
- **Maintenance Dose:** 12 mg every four months
- **Pediatric Considerations:** Dosage is generally the same for pediatric patients

### Side Effects

- **Common:** Headache, back pain, post-lumbar puncture syndrome
- **Serious:** Respiratory infections, coagulation abnormalities, hydrocephalus

### Contraindications

- **Hypersensitivity:** To nusinersen or its components
- **Coagulation Disorders:** Due to intrathecal administration

#### Monitoring

- **Liver Function:** Periodic liver function tests
- **Coagulation Parameters:** Before each dose
- **Respiratory Function:** Especially in patients with compromised respiratory function

#### Cost-Effectiveness

- **High Cost:** Approximately \$750,000 for the first year, \$375,000 annually thereafter; this is the major limitation for its widespread use especially in second and third world countries
- **Cost-Benefit Analysis:** Improved quality of life and reduced healthcare utilization for SMA patients

#### Future Directions

- **Ongoing Trials:** For non-ambulatory SMA patients, combination therapies
- **Pharmacoeconomic Studies:** To evaluate long-term cost-effectiveness

#### Onasemnogene Apeparvovec (Zolgensma)

- **Mechanism:** Gene therapy that delivers a functional copy of the SMN1 gene
- **Administration:** Intravenous
- **Efficacy:** Long-term improvement in motor function
- **Side Effects:** Elevated liver enzymes, vomiting
- **Cost:** Extremely high; around \$2.1 million for a one-time treatment

#### Risdiplam (Evrysdi)

- **Mechanism:** Small molecule that increases SMN protein production
- **Administration:** Oral
- **Efficacy:** Improved motor milestones
- **Side Effects:** Fever, diarrhea, rash



- **Cost:** Lower than gene therapy but still significant; around \$340,000 per year

#### Supportive Therapies

- **Respiratory Support**
  - **Mechanism:** Non-invasive ventilation, cough assist devices
  - **Goal:** Prevent respiratory failure and improve quality of life
- **Nutritional Support**
  - **Mechanism:** Gastrostomy, high-calorie diets
  - **Goal:** Prevent malnutrition and support growth
- **Physical Therapy**
  - **Mechanism:** Range-of-motion exercises, adaptive equipment
  - **Goal:** Improve mobility and prevent contractures
- **Orthopedic Interventions**
  - **Mechanism:** Bracing, surgical correction of deformities
  - **Goal:** Improve posture and mobility

#### Experimental Therapies

- **SMN-Inducing Compounds**
  - **Mechanism:** Small molecules that upregulate SMN protein
  - **Status:** Clinical trials
- **Stem Cell Therapy**
  - **Mechanism:** Transplantation of stem cells to replace damaged motor neurons
  - **Status:** Pre-clinical studies

#### Future Directions

- **Combination Therapies**
  - **Rationale:** Synergistic effects of gene therapy and antisense oligonucleotides
  - **Status:** Under investigation
- **Biomarker Development**

- **Rationale:** Early diagnosis and treatment monitoring
- **Status:** Ongoing research

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## 2. a) Modified Jones Diagnostic criteria for rheumatic fever in children.

### • **Major Criteria**

- **Carditis:** Clinical or subclinical evidence of inflammation affecting the heart, often manifesting as valvulitis, myocarditis, or pericarditis.
- **Polyarthritits:** Migratory inflammation affecting large joints like the knees, ankles, elbows, and wrists.
- **Chorea:** Neurological disorder characterized by rapid, involuntary movements, primarily affecting the face, feet, and hands.
- **Erythema Marginatum:** Non-pruritic rash with erythematous margins and clear centers, often occurring on the trunk or limbs.
- **Subcutaneous Nodules:** Painless, firm nodules overlying bony prominences or tendons, commonly found on the extensor surfaces.

### • **Minor Criteria**

- **Fever:** Elevated body temperature, usually above 38.5°C.
- **Arthralgia:** Joint pain without evidence of actual inflammation.
- **Elevated Acute Phase Reactants:** Elevated levels of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR).
- **Prolonged PR Interval:** Demonstrated on electrocardiogram (ECG), not applicable if carditis is a major criterion.
- **Previous Rheumatic Fever or Rheumatic Heart Disease:** A history of either condition can serve as a minor criterion.

### • **Supporting Evidence**

- **Positive Throat Culture or Rapid Antigen Test:** For Group A Streptococcus (GAS).
- **Rising or Elevated Anti-Streptolysin O (ASO) or Other Streptococcal Antibodies:** Such as anti-DNase B.



- **Diagnostic Requirements**

- **Initial Episode:** Two major criteria, or one major and two minor criteria, along with evidence of a preceding streptococcal infection.
- **Recurrent Episode:** Two major criteria, or one major and two minor criteria, or three minor criteria, along with evidence of a preceding streptococcal infection.

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## 2. b) Newer drugs in the treatment of cystic fibrosis.

- ❖ The introduction of CFTR modulators has revolutionized the treatment of CF, transforming it from a disease focused on symptom management to one where the underlying cause can be addressed
- ❖ These therapies have significantly improved the prognosis and quality of life for many people with CF
- ❖ However, challenges remain, including ensuring access to these therapies, understanding long-term effects, and developing treatments for all CFTR mutations
- ❖ Regular monitoring and a multidisciplinary approach remain crucial in the management of CF patients.

### 1. **CFTR Modulators:**

- These drugs target the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is dysfunctional in CF.

### 2. **Ivacaftor (Kalydeco):**

- **Mechanism:** Potentiator that enhances the function of the CFTR protein at the cell surface.
- **Indication:** Patients with specific CFTR mutations (G551D and others).
- **Impact:** Improves lung function and reduces pulmonary exacerbations.

### 3. **Lumacaftor/Ivacaftor (Orkambi):**

- **Mechanism:** Lumacaftor is a corrector that helps the CFTR protein fold properly, while ivacaftor is a potentiator.
- **Indication:** Patients homozygous for the F508del mutation.
- **Impact:** Improves lung function and quality of life.

#### 4. **Tezacaftor/Ivacaftor (Symdeko/Symkevi):**

- **Mechanism:** Combination of a corrector (tezacaftor) and a potentiator (ivacaftor).
- **Indication:** Patients with F508del mutation and certain other mutations.
- **Impact:** Similar benefits to lumacaftor/ivacaftor but with a better side effect profile.

#### 5. **Elexacaftor/Tezacaftor/Ivacaftor (Trikafta/Kaftrio):**

- **Mechanism:** Triple combination therapy that includes two correctors (elexacaftor and tezacaftor) and a potentiator (ivacaftor).
- **Indication:** Patients with at least one F508del mutation.
- **Impact:** Significantly improves lung function, reduces exacerbations, and improves quality of life. Considered a breakthrough in CF treatment.

#### 6. **Gene Therapy and Gene Editing:**

- **Research Stage:** Experimental approaches aiming to correct or replace the defective CFTR gene.
- **Potential:** Could offer a more definitive treatment for CF in the future.

#### **Research and Future Directions:**

- **Personalized Medicine:** Ongoing research is focused on developing treatments tailored to specific CFTR mutations.
- **Combination Therapies:** Exploring combinations of different modulators to maximize efficacy.
- **Gene Editing:** CRISPR and other gene-editing technologies hold promise for potentially curing CF by directly correcting the genetic defect.

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### 3. a) **Recent advances in management of childhood asthma.**

- ❖ Recent advances in the management of childhood asthma reflect a deeper understanding of the disease's pathophysiology, leading to more personalized and effective treatment strategies
- ❖



- ❖ The management of childhood asthma is rapidly evolving, with a shift towards more personalized, phenotype/endotype-driven approaches
- ❖ Biologic therapies have opened new avenues for treating severe asthma, and digital health technologies are improving asthma management and patient education
- ❖ Ongoing research and updated guidelines continue to refine treatment strategies, emphasizing early intervention, prevention, and the importance of maintaining good asthma control.

### 1. Biologic Therapies:

- **Omalizumab (Anti-IgE Therapy):** Used for severe allergic asthma. Reduces exacerbations and steroid use.
- **Mepolizumab and Reslizumab (Anti-IL-5 Therapies):** Target eosinophilic inflammation, suitable for severe eosinophilic asthma.
- **Benralizumab (Anti-IL-5 Receptor Alpha):** Also for severe eosinophilic asthma, reduces exacerbations and oral corticosteroid use.
- **Dupilumab (Anti-IL-4Rα):** Targets the IL-4 and IL-13 pathways, effective in severe asthma with an allergic component or with eosinophilic inflammation.

### 2. Phenotype-Endotype Driven Treatment:

- Understanding that asthma is not a single disease but a collection of various phenotypes and endotypes has led to more tailored treatments.
- Biomarkers like blood eosinophils, fractional exhaled nitric oxide (FeNO), and serum IgE levels help in identifying specific asthma phenotypes and guiding therapy.

### 3. Smart Inhalers and Digital Health:

- Smart inhalers equipped with sensors track medication use and inhaler technique, improving adherence and control.
- Integration with smartphone apps and telemedicine for better monitoring and patient education.

### 4. Updated Guidelines:

- **Global Initiative for Asthma (GINA) 2021 Update:** Emphasizes the importance of inhaled corticosteroids (ICS) in all patients with asthma, even for occasional use.
- Recommends against using short-acting beta-agonists (SABAs) alone without ICS due to risk of severe exacerbations.

### 5. Early Intervention and Prevention:

- Focus on early-life interventions, including modifying environmental factors and early use of ICS in high-risk children to prevent asthma development and progression.

### 6. Bronchial Thermoplasty:

- For severe asthma not controlled by pharmacological treatment. It reduces airway smooth muscle mass, decreasing bronchoconstriction.

### 7. Personalized Medicine:

- Genetic studies are contributing to a better understanding of individual responses to asthma medications, paving the way for personalized medicine.

### 8. Vitamin D Supplementation:

- Emerging evidence suggests that vitamin D supplementation may improve asthma control, especially in patients with low vitamin D levels.

### 9. Environmental Control and Allergen Immunotherapy:

- Enhanced focus on controlling environmental triggers.
- Allergen-specific immunotherapy for allergic asthma, especially effective in children with allergic rhinitis and asthma.

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### 3. b) Role of Zn, Cu and Mg in nutrition and disease.

- ❖ The balance of these trace elements is crucial for health. Deficiencies or excesses can lead to a range of health issues.
- ❖ Dietary sources are usually sufficient to meet the body's needs, but in certain conditions or diseases, supplementation may be necessary.
- ❖ It's important to approach supplementation cautiously, as excessive intake can have adverse effects. Regular monitoring and a balanced diet are key to maintaining optimal levels of these essential nutrients.

#### Zinc (Zn):

##### 1. Immune Function:

- Crucial for normal development and function of cells mediating innate immunity.



- Deficiency impairs immune response, increasing susceptibility to infections.

## 2. **Enzymatic Reactions:**

- A cofactor for over 300 enzymes involved in DNA synthesis, cell division, protein synthesis, and wound healing.

## 3. **Growth and Development:**

- Essential for growth and development, particularly during pregnancy, childhood, and adolescence.

## 4. **Disease Associations:**

- Deficiency can lead to growth retardation, delayed sexual maturation, infection susceptibility, hair loss, and impaired wound healing.
- Excess zinc can lead to copper deficiency, neurological problems, and gastrointestinal disturbances.

### **Copper (Cu):**

#### 1. **Enzymatic Reactions:**

- Integral part of several enzymes (cuproenzymes) involved in energy production, iron metabolism, connective tissue formation, and neurotransmitter synthesis.

#### 2. **Iron Metabolism:**

- Essential for the absorption and metabolism of iron, playing a role in red blood cell formation.

#### 3. **Antioxidant Defense:**

- Component of ceruloplasmin and superoxide dismutase, enzymes important in antioxidant defense.

#### 4. **Disease Associations:**

- Deficiency can cause anemia, neutropenia, bone abnormalities, and cardiovascular disease.
- Wilson's disease is a genetic disorder leading to copper accumulation, causing liver and brain damage.
- Menkes disease is a genetic disorder of copper deficiency affecting males, leading to growth failure, neurological problems, and death in early childhood.

### **Magnesium (Mg):**

#### **1. Enzymatic Reactions:**

- Cofactor in over 300 enzymatic reactions, including those involved in energy metabolism, protein synthesis, and cell signaling.

#### **2. Muscle and Nerve Function:**

- Plays a key role in nerve transmission and muscle contraction.

#### **3. Bone Health:**

- Important for bone structure; influences the bone mineral matrix and bone metabolism.

#### **4. Cardiovascular Health:**

- Essential for maintaining normal heart rhythm and is used in managing certain heart conditions.

#### **5. Disease Associations:**

- Deficiency can lead to muscle cramps, seizures, osteoporosis, cardiovascular disease, and metabolic syndrome.
- Excess intake can cause diarrhea, and in extreme cases, heart problems.

| Role in Nutrition                                                                                                                                                                                                                                                                                           | Role in Disease                                                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Zinc (Zn)</b>                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>• Essential for immune function, enzyme activity, DNA synthesis, and cell division.</li> <li>• Important for growth and development, especially in pregnancy, childhood, and adolescence.</li> </ul>                                                                 | <ul style="list-style-type: none"> <li>• Deficiency: Growth retardation, delayed sexual maturation, increased infection susceptibility, hair loss, impaired wound healing.</li> <li>• Excess: Can lead to copper deficiency, neurological issues, gastrointestinal disturbances.</li> </ul>                                                                       |
| <b>Copper (Cu)</b>                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>• Integral to enzymes involved in energy production, iron metabolism, connective tissue formation, and neurotransmitter synthesis.</li> <li>• Important for iron absorption and red blood cell formation.</li> <li>• Plays a role in antioxidant defense.</li> </ul> | <ul style="list-style-type: none"> <li>• Deficiency: Anemia, neutropenia, bone abnormalities, cardiovascular issues.</li> <li>• Wilson's disease: Genetic disorder causing copper accumulation, leading to liver and brain damage.</li> <li>• Menkes disease: Genetic disorder of copper deficiency, causing growth failure and neurological problems.</li> </ul> |



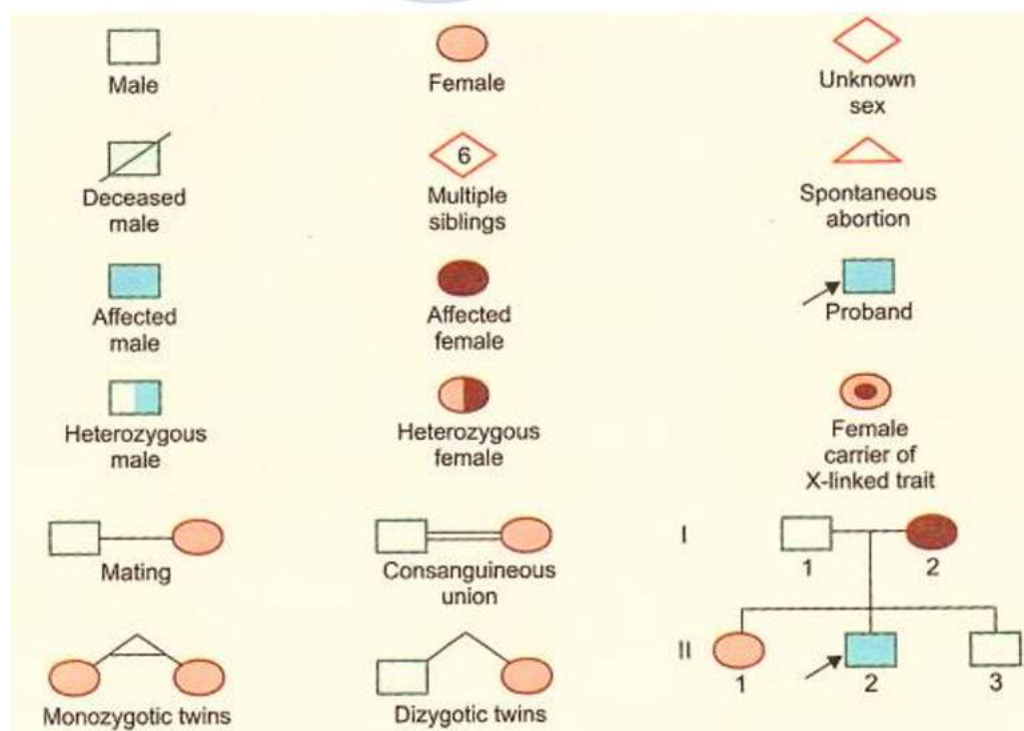
### Magnesium (Mg)

- |                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Cofactor in over 300 enzymatic reactions, including energy metabolism, protein synthesis, and cell signaling.</li> <li>• Crucial for muscle and nerve function, bone health, and cardiovascular health.</li> </ul> | <ul style="list-style-type: none"> <li>• Deficiency: Muscle cramps, seizures, osteoporosis, cardiovascular disease, metabolic syndrome.</li> <li>• Excess: Can cause diarrhea and, in extreme cases, heart problems.</li> </ul> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

- **Dietary Sources:** A balanced diet typically provides adequate amounts of these trace elements. Zinc is found in meat, shellfish, legumes, and seeds. Copper is present in organ meats, seafood, nuts, and seeds. Magnesium is abundant in leafy greens, nuts, seeds, and whole grains.
- **Supplementation:** Should be considered carefully and under medical guidance, especially in cases of deficiency or specific health conditions.
- **Interactions:** These elements can interact with each other and with other nutrients, affecting absorption and utilization. For example, high doses of zinc can interfere with copper absorption.

#### 4. a) Pedigree chart and patterns of inheritance

**Pedigree Chart representation conventions:**



## Mendelian Inheritance Patterns

### 1. *Autosomal Dominant Inheritance*

- Single copy of mutated gene sufficient for phenotype expression.
- Vertical transmission through generations.
- Examples: Huntington's disease, Marfan syndrome.

### 2. *Autosomal Recessive Inheritance*

- Two copies of mutated gene required for phenotype expression.
- Often seen in consanguineous families.
- Examples: Cystic fibrosis, Sickle cell anemia.

### 3. *X-linked Dominant Inheritance*

- Mutation on X chromosome; males more severely affected.
- Vertical transmission but often absent in successive male generations.
- Examples: Rett syndrome, Fragile X syndrome.

### 4. *X-linked Recessive Inheritance*

- Mutation on X chromosome; males predominantly affected.
- Skips generations; carrier females often asymptomatic.
- Examples: Hemophilia, Duchenne muscular dystrophy.

### 5. *Y-linked Inheritance*

- Mutation on Y chromosome; only males affected.
- Direct male-to-male transmission.
- Examples: Y-linked infertility, Swyer syndrome.

## Non-Mendelian Inheritance Patterns

### 1. *Mitochondrial Inheritance*

- Maternal transmission; both sexes affected.
- Examples: Leber's hereditary optic neuropathy, Mitochondrial myopathy.

### 2. *Codominant Inheritance*



- Both alleles contribute to the phenotype.
- Examples: Blood type AB, Sickle cell trait.

### 3. **Polygenic Inheritance**

- Multiple genes contribute to phenotype.
- Examples: Height, skin color.

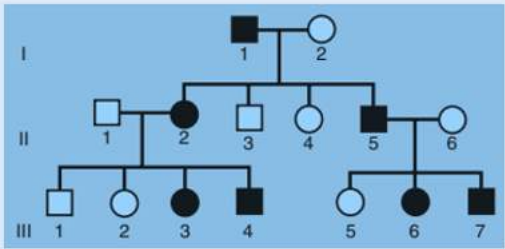
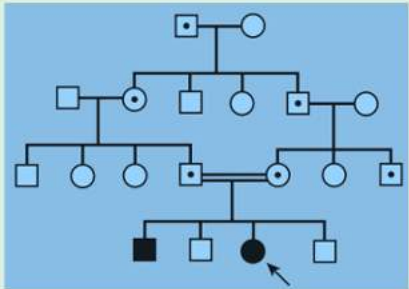
### 4. **Epigenetic Inheritance**

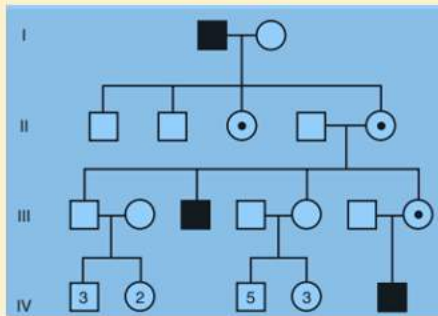
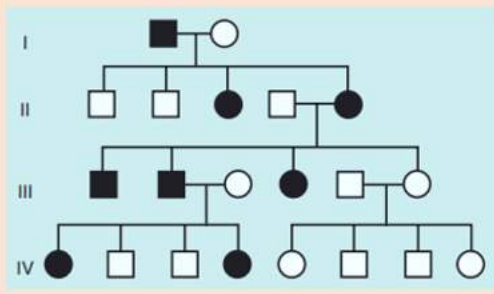
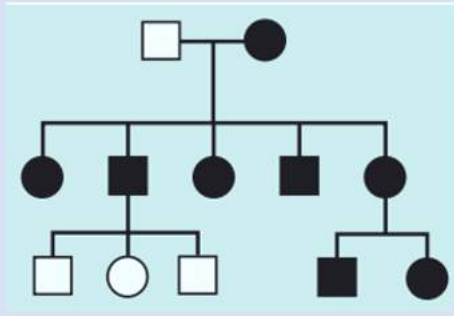
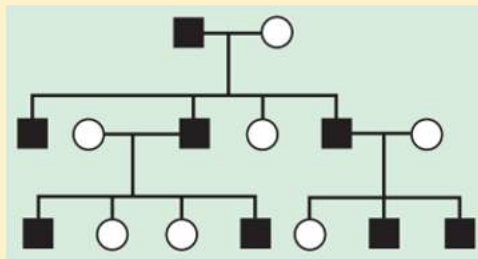
- Modifications in gene expression, not DNA sequence.
- Examples: Genomic imprinting, X-inactivation.

### 5. **Genomic Imprinting**

- Expression depends on parent-of-origin.
- Examples: Prader-Willi syndrome, Angelman syndrome.

Each pattern of inheritance has unique characteristics that influence how genetic conditions and traits are passed through families.

| Pattern of Inheritance/ Pedigree                                                                                 | Key Attributes                                                             | Gender Affected | Generation Skipping | Examples                              |
|------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------|---------------------|---------------------------------------|
| <b>Autosomal Dominant</b><br>  | One affected parent; 50% chance of passing the gene; variable expressivity | Both            | No                  | Huntington's disease, Marfan syndrome |
| <b>Autosomal Recessive</b><br> | Parents usually carriers; 25% risk for each child; can skip generations    | Both            | Yes                 | Cystic fibrosis, Sickle cell anemia   |

|                                                                                                               |                                                                                                                                        |                 |          |                                                                      |
|---------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|-----------------|----------|----------------------------------------------------------------------|
| <b>X-linked Recessive</b><br> | Mostly affects males;<br>carrier mothers; no<br>father-to-son<br>transmission                                                          | Mostly<br>Males | Possible | Hemophilia,<br>Duchenne<br>muscular<br>dystrophy                     |
| <b>X-linked Dominant</b><br>  | Both genders affected;<br>affected fathers pass to<br>all daughters; carrier<br>mothers have 50%<br>chance of passing to<br>each child | Both            | No       | Fragile X<br>syndrome, Rett<br>syndrome                              |
| <b>Mitochondrial</b><br>    | Maternal transmission;<br>variable expression;<br>affects both genders,<br>but only females pass<br>it on                              | Both            | No       | Leber's hereditary<br>optic neuropathy,<br>Mitochondrial<br>myopathy |
| <b>Y-linked</b><br>         | Only affects males;<br>passed from father to<br>all sons                                                                               | Only<br>Males   | No       | Y-chromosome<br>infertility, Male<br>pattern baldness                |

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#### 4. b) Human milk banking

- ✚ Human milk banking plays a crucial role in providing the benefits of human milk to infants who would otherwise not have access to it. The process is carefully regulated to ensure the safety and health of both donors and recipients.
- ✚ Human milk banking is a service that collects, screens, processes, and dispenses donated human milk. It's a valuable resource for infants who cannot be breastfed by their own mothers due to various reasons, such as illness, medication use, or low milk supply.

##### *Criteria for Donors*

- **Health Status:** Must be in good general health, non-smokers, and free from chronic illnesses.
- **Lifestyle:** No use of illegal drugs, no alcohol consumption within a certain period before donation, and limited or no intake of caffeine.
- **Medications:** Not taking any medication, including certain herbal supplements, except for birth control or replacement thyroid hormone.
- **Blood Screening:** Tested for HIV, HTLV, Hepatitis B and C, syphilis, and other infectious diseases.
- **Breast Milk Supply:** Must have an ample supply of milk and be willing to donate a minimum amount.
- **Infant's Health:** The donor's own infant must be healthy and gaining weight appropriately.
- **Diet:** A well-balanced diet is recommended for milk donors.
- **Informed Consent:** Must provide informed consent after being educated about the milk banking process.

##### *Collection Process*

- **Hygiene:** Thorough handwashing and breast cleaning before expressing milk.
- **Pumping Equipment:** Use of sterilized breast pumps and collection containers.
- **Expressing Milk:** Following safe milk expression practices to avoid contamination.
- **Labeling:** Clearly labeling milk with the date and time of expression.

##### *Storage of Donated Milk*

- **Temperature Control:** Freshly expressed milk should be chilled immediately and frozen within 24 hours.
- **Freezing:** Milk is stored in a freezer at temperatures of -20°C (-4°F) or colder.
- **Duration:** Frozen milk can be stored for up to 6 months, though some banks prefer a shorter duration.
- **Transport:** Milk is transported to the milk bank in insulated coolers with ice packs to maintain the cold chain.

### **At the Milk Bank**

- **Screening:** Upon arrival, milk is thawed and pooled with milk from other donors to ensure a mix of nutrients.
- **Pasteurization:** Milk is pasteurized using the Holder method (62.5°C for 30 minutes) to kill any bacteria or viruses without significantly damaging the nutritional and immunological quality of the milk.
- **Testing:** After pasteurization, milk is tested for bacterial contamination.
- **Storage After Pasteurization:** Pasteurized milk is quickly frozen and stored until dispensed.
- **Tracking:** Milk banks keep detailed records to track each batch of milk from donor to recipient.

### **Dispensing**

- **Prescription:** Donor milk is often dispensed based on a prescription for infants in need.
- **Priority:** Premature and ill infants in hospitals often have priority for donor milk.
- **Outpatient Use:** Some milk banks also provide milk for outpatient use, often for premature infants after discharge or for those with medical conditions.

### **Safety and Quality Assurance**

- **Regular Monitoring:** Milk banks regularly monitor and review their processes to ensure safety and quality.
- **Accreditation:** Many milk banks operate under the guidelines and accreditation of the [Human Milk Banking Association of North America \(HMBANA\)](#) or similar organizations in other countries.

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### 5. a) Role of oxygen free radicals in diseases

- **Research and Trials:** Ongoing studies are exploring the efficacy of antioxidants in various pediatric conditions.
- **Individualized Approach:** Management strategies should be tailored to the specific needs and conditions of pediatric patients.

| Disease Category                                    | Role of ROS                           | Specific Mechanisms and Effects                                                                                        | Clinical Implications and Management                                                                              |
|-----------------------------------------------------|---------------------------------------|------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| <b>Neonatal Respiratory Distress Syndrome (RDS)</b> | Lung Injury, Inflammation             | ROS contribute to lung tissue damage and inflammation.<br>Exacerbates surfactant deficiency effects.                   | Antioxidant therapy may be beneficial.<br>Focus on minimizing oxidative stress in ventilatory support.            |
| <b>Bronchopulmonary Dysplasia (BPD)</b>             | Chronic Lung Disease                  | ROS implicated in lung injury and impaired development.<br>Aggravated by oxygen therapy and inflammation.              | Antioxidant strategies in prevention and management.<br>Careful oxygen administration to minimize ROS production. |
| <b>Retinopathy of Prematurity (ROP)</b>             | Retinal Damage                        | High oxygen levels lead to ROS production, damaging retinal vessels.<br>Contributes to abnormal vessel growth.         | Monitoring oxygen therapy to prevent hyperoxia.<br>Potential role of antioxidants in prevention.                  |
| <b>Necrotizing Enterocolitis (NEC)</b>              | Intestinal Injury                     | ROS play a role in intestinal inflammation and necrosis.<br>Ischemia-reperfusion injury contributes to ROS generation. | Antioxidant supplementation as a potential adjunct therapy.<br>Focus on reducing intestinal oxidative stress.     |
| <b>Pediatric Cancers</b>                            | Tumor Progression, Treatment Response | ROS can induce DNA damage leading to oncogenesis.<br>Affects chemotherapy and radiation therapy responses.             | Exploring ROS modulation in cancer treatment.<br>Antioxidant role in reducing therapy-related oxidative damage.   |

|                                          |                                               |                                                                                                                   |                                                                                                                           |
|------------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| <b>Neurodevelopmental Disorders</b>      | Neuronal Damage, Cognitive Impairment         | Oxidative stress implicated in conditions like autism, ADHD. Affects neuronal development and function.           | Investigating antioxidant therapy in management. Focus on reducing oxidative stress in early development.                 |
| <b>Pediatric Cardiovascular Diseases</b> | Cardiomyopathy, Hypertension                  | ROS contribute to myocardial stress and hypertension. Affects cardiac function and vascular health.               | Antioxidant therapy in conjunction with standard treatments. Lifestyle modifications to reduce oxidative stress.          |
| <b>Juvenile Diabetes (Type 1)</b>        | $\beta$ -cell Destruction, Insulin Resistance | Autoimmune destruction of $\beta$ -cells linked with oxidative stress. ROS affect insulin signaling pathways.     | Antioxidant supplementation as part of diabetes management. Research on reducing oxidative stress in diabetes prevention. |
| <b>Pediatric Rheumatic Diseases</b>      | Joint Inflammation, Damage                    | ROS involved in inflammatory processes in diseases like juvenile arthritis. Contributes to joint damage and pain. | Antioxidant therapy as an adjunct to anti-inflammatory treatment. Focus on diet and lifestyle to manage oxidative stress. |
| <b>Inherited Metabolic Disorders</b>     | Cellular Dysfunction, Organ Damage            | ROS play a role in the pathogenesis of disorders like mitochondrial diseases. Affects cellular energy metabolism. | Antioxidant supplementation as a potential treatment. Managing oxidative stress in metabolic therapies.                   |

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## 5. b) Indications of growth hormone replacement therapy.

### 1. Growth Hormone Deficiency (GHD)

- Confirmed deficiency through GH stimulation tests
- Short stature with slow growth velocity
- Congenital GHD due to genetic mutations or structural abnormalities



## 2. Idiopathic Short Stature (ISS)

- Height significantly below the mean for age and sex
- Absence of other identifiable causes of short stature

## 3. Turner Syndrome

- Confirmed diagnosis through karyotype analysis
- Short stature commonly associated with the syndrome

## 4. Prader-Willi Syndrome

- Genetic confirmation of the syndrome
- Short stature, hypotonia, and developmental delays

## 5. Chronic Renal Insufficiency

- Growth failure despite optimal medical management
- Pre-transplant patients to improve growth outcomes

## 6. Small for Gestational Age (SGA)

- Birth weight and/or length below -2 SD for gestational age
- Failure to catch-up growth by age 2-4 years

## 7. Noonan Syndrome

- Confirmed diagnosis through genetic testing
- Associated growth failure

## 8. SHOX Gene Haploinsufficiency

- Short stature homeobox-containing gene deficiency
- Short stature with or without skeletal abnormalities

## 9. Cachexia or Muscle Wasting Conditions

- Conditions like HIV-associated muscle wasting
- Severe burns or major surgeries leading to catabolic states

## 10. Cystic Fibrosis

- Growth failure despite optimal nutritional and medical management

## 11. Intrauterine Growth Retardation (IUGR)

- Persistent growth failure postnatally

## 12. Pubertal Delay

- Delayed puberty with associated growth failure

### Contraindications

- Active malignancy
- Closed epiphyses
- Severe obesity
- Uncontrolled diabetes

### Precautions

- Regular monitoring of glucose levels due to potential diabetogenic effect
- Monitoring of thyroid function, as GH can induce hypothyroidism
- Monitoring for signs of intracranial hypertension

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## 6. a) Explain the anatomical and functional factors for obstructive sleep apnoea

- ❖ Obstructive Sleep Apnea (OSA) in both adults and children is a disorder characterized by repeated episodes of partial or complete obstruction of the upper airway during sleep, leading to disrupted sleep and decreased oxygenation.
- ❖ The pathophysiology of OSA is complex, involving an interplay of anatomical and functional factors.
- ❖ These factors can vary significantly between individuals, and their relative contributions can change over time.
- ❖ Understanding these factors is crucial for effective management, which may include lifestyle changes, surgical interventions, and the use of continuous positive airway pressure (CPAP) therapy.

### Anatomical Factors:

#### 1. Upper Airway Anatomy:

- **Narrowed Airway:** Individuals with a naturally narrow or collapsible upper airway are at higher risk.



- **Adenotonsillar Hypertrophy:** Common in children; enlarged tonsils and adenoids can obstruct the airway.
- **Craniofacial Abnormalities:** Conditions like retrognathia or micrognathia (small jaw) can lead to airway obstruction.
- **Obesity:** Excess fat deposits around the neck and throat can narrow the airway.
- **Nasal Obstruction:** Deviated septum, chronic nasal congestion, and polyps can contribute to OSA.

## 2. **Soft Tissue Factors:**

- **Tongue Size:** A large tongue can block the airway during sleep.
- **Palate Structure:** A long, soft palate or uvula can narrow the airway.

## **Functional Factors:**

### 1. **Muscle Tone:**

- **Reduced Muscle Tone During Sleep:** Muscle relaxation during sleep can lead to airway collapse, especially in the presence of anatomical predispositions.
- **Neuromuscular Disorders:** Conditions that affect muscle tone can increase OSA risk.

### 2. **Respiratory Control:**

- **Ventilatory Control Instability:** Variability in respiratory control can lead to periods of hypoventilation and apnea.

### 3. **Sleep Position:**

- **Supine Position:** Sleeping on the back can worsen OSA due to gravitational effects on the airway.

### 4. **Endocrine and Metabolic Factors:**

- **Hormonal Imbalances:** Conditions like hypothyroidism can contribute to OSA.
- **Insulin Resistance and Diabetes:** Associated with OSA, possibly due to shared risk factors like obesity.

## **Age-Related Factors:**

- **Children:** Adenotonsillar hypertrophy is a major factor. Obesity is increasingly recognized as a contributor.
- **Adults:** Obesity, craniofacial abnormalities, and age-related changes in airway anatomy and muscle tone are significant factors.

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## 6. b) How will you diagnose and treat OSA?

- ❖ Diagnosing and treating Obstructive Sleep Apnea (OSA) involves a comprehensive approach that includes clinical evaluation, diagnostic testing, and a range of therapeutic options tailored to the severity of the condition and the individual patient's needs
- ❖ The diagnosis and treatment of OSA require a multidisciplinary approach, considering the individual patient's symptoms, severity of OSA, and presence of comorbid conditions
- ❖ Treatment aims to improve sleep quality, reduce daytime symptoms, and prevent long-term health complications
- ❖ Continuous follow-up and adjustment of therapy are essential for effective management.

### Diagnosis of OSA:

#### 1. **Clinical Evaluation:**

- **Symptom Assessment:** Common symptoms include loud snoring, observed episodes of breathing cessation during sleep, daytime sleepiness, morning headaches, and irritability.
- **Medical and Sleep History:** Assessment of risk factors like obesity, neck circumference, family history, and comorbidities (e.g., hypertension, diabetes).
- **Physical Examination:** Focuses on the upper airway, including the nasal passages, oropharynx, and neck. Examination for signs of adenotonsillar hypertrophy in children.

#### 2. **Sleep Studies:**

- **Polysomnography (PSG):** The gold standard for OSA diagnosis. Conducted overnight in a sleep lab, it monitors sleep stages, breathing, oxygen levels, heart rate, and muscle activity.



- **Home Sleep Apnea Testing (HSAT):** A simplified version of PSG, suitable for some patients, conducted at home.

### 3. **Other Diagnostic Tools:**

- **Epworth Sleepiness Scale:** A questionnaire assessing daytime sleepiness.
- **Imaging:** Rarely used but can include cephalometric X-rays or MRI to assess airway anatomy.

## Treatment of OSA:

### 1. **Lifestyle Modifications:**

- **Weight Loss:** Especially important in obese patients.
- **Sleep Position Training:** Avoiding supine sleep can reduce apnea episodes.
- **Avoidance of Alcohol and Sedatives:** These can exacerbate OSA by relaxing throat muscles.

### 2. **Continuous Positive Airway Pressure (CPAP):**

- **Primary Treatment:** Especially for moderate to severe OSA.
- **Mechanism:** Delivers air through a mask to keep the airway open during sleep.
- **Adherence:** Patient education and follow-up are crucial for adherence.

### 3. **Oral Appliances:**

- **Mandibular Advancement Devices (MADs):** Common in mild to moderate OSA. They advance the lower jaw forward to keep the airway open.
- **Tongue-Retaining Devices:** Less commonly used.

### 4. **Surgical Options:**

- **Uvulopalatopharyngoplasty (UPPP):** Removal of excess tissue in the throat.
- **Maxillomandibular Advancement (MMA):** Repositioning the jaw to enlarge the airway.
- **Adenotonsillectomy:** Particularly in children with adenotonsillar hypertrophy.

- **Nasal Surgery:** For patients with significant nasal obstruction.
- 5. **Positional Therapy:**
  - **For Positional OSA:** Devices that prevent sleeping on the back.
- 6. **Positive Airway Pressure (PAP) Alternatives:**
  - **BiPAP:** Beneficial for patients who struggle with CPAP.
  - **Auto-CPAP (APAP):** Automatically adjusts pressure.
- 7. **Management of Comorbidities:**
  - **Addressing Associated Conditions:** Like diabetes, hypertension, and heart disease.
- 8. **ENT Considerations:**
  - **Focus on Adenotonsillar Hypertrophy:** Adenotonsillectomy is often the first-line treatment.
  - **Weight Management:** In obese children.
  - **Orthodontic Interventions:** In cases of craniofacial abnormalities.

#### **Monitoring and Follow-Up:**

- **Regular Follow-Up:** To assess treatment efficacy and adherence.
- **Adjustment of Treatment:** Based on symptom improvement and patient comfort.
- **Long-Term Management:** OSA is typically a chronic condition requiring ongoing management.

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#### **7. a) Components of Nutritional Rehabilitation Centres.**

- ❖ Nutritional Rehabilitation Centers (NRCs) play a crucial role in addressing severe malnutrition, particularly in resource-limited settings
- ❖ These centers are designed to provide comprehensive care for malnourished children, integrating medical treatment with nutritional rehabilitation and caregiver education
- ❖ Nutritional Rehabilitation Centers are vital in the fight against child malnutrition, providing a multifaceted approach that goes beyond mere calorie provision



- ❖ They offer a blend of medical care, nutritional rehabilitation, education, and psychosocial support, crucial for the holistic recovery and long-term well-being of malnourished children

1. **Medical Assessment and Treatment:**

- **Initial Medical Evaluation:** To identify and treat underlying medical conditions contributing to malnutrition.
- **Regular Monitoring:** Vital signs, growth parameters, and clinical status are monitored regularly.
- **Treatment of Complications:** Addressing issues like infections, electrolyte imbalances, and organ dysfunction.

2. **Nutritional Rehabilitation:**

- **Therapeutic Feeding:** Using specially formulated diets (e.g., F-75, F-100 therapeutic milk) to gradually and safely restore nutritional status.
- **Transition to Solid Foods:** Gradual introduction of age-appropriate, nutrient-dense foods.
- **Monitoring Nutritional Progress:** Regular assessment of weight gain and nutritional status.

3. **Psychosocial Support and Counseling:**

- **Counseling for Caregivers:** Education on child nutrition, feeding practices, and hygiene.
- **Psychosocial Support:** For children and families, addressing the psychological aspects of malnutrition and hospitalization.

4. **Health and Nutrition Education:**

- **Disease Prevention:** Education on preventing common childhood illnesses and malnutrition.
- **Nutrition Education:** Teaching about balanced diets, food preparation, and feeding practices.
- **Hygiene and Sanitation:** Instruction on basic hygiene practices to prevent infection.

5. **Facilities and Infrastructure:**

- **Inpatient Care:** Adequate facilities for the care of severely malnourished children.
- **Outpatient Services:** For follow-up and continued care post-discharge.
- **Kitchen and Food Preparation Areas:** Hygienic spaces for preparing therapeutic foods.

6. **Staff and Training:**

- **Skilled Healthcare Professionals:** Including doctors, nurses, nutritionists, and support staff.
- **Ongoing Training:** Regular training on the latest protocols and practices in nutritional rehabilitation.

7. **Community Integration and Follow-Up:**

- **Community Outreach:** Programs to identify and refer malnourished children to the NRC.
- **Follow-Up Care:** Post-discharge monitoring to prevent relapse and ensure sustained recovery.

8. **Research and Monitoring:**

- **Data Collection and Analysis:** For monitoring outcomes and improving care protocols.
- **Participation in Research:** Contributing to the broader understanding of malnutrition and its management.

9. **Collaboration and Coordination:**

- **Networking with Other Health Services:** Ensuring a continuum of care for children with complex needs.
- **Coordination with Government and NGOs:** For support, funding, and policy development.

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### 7. b) Enumerate the differences between Hirschsprung disease and functional constipation.

- ❖ While both Hirschsprung disease and functional constipation present with constipation and bowel movement difficulties, they are fundamentally different in their etiology, presentation, and management
- ❖ Hirschsprung disease is a congenital anomaly requiring surgical intervention, whereas functional constipation is typically managed with lifestyle modifications and medical management
- ❖ Accurate diagnosis is crucial for appropriate treatment and management of these conditions.

| Parameter                   | Hirschsprung Disease                                                                                                                                                              | Functional Constipation                                                                                                                                         |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Definition</b>           | A congenital disorder where nerve cells (ganglion cells) are absent in a segment of the bowel, leading to bowel obstruction and difficulty passing stool.                         | A common condition characterized by infrequent bowel movements or difficult passage of stools that is not due to any underlying physical abnormality.           |
| <b>Age of Onset</b>         | Symptoms often present in newborns or early infancy.                                                                                                                              | Can occur at any age, but often begins when introducing solid foods, toilet training, or school entry.                                                          |
| <b>Symptoms</b>             | Delayed passage of meconium.<br>Chronic constipation starting in infancy.<br>Abdominal distension.<br>Vomiting.<br>Failure to thrive.                                             | Infrequent bowel movements.<br>Straining during bowel movements.<br>Hard or pellet-like stools.<br>Occasional soiling or fecal incontinence.<br>Abdominal pain. |
| <b>Physical Examination</b> | Tight anal sphincter.<br>Empty rectum on digital rectal examination.<br>Abdominal distension.                                                                                     | Normal anal sphincter tone.<br>Possible presence of a large fecal mass in the rectum.<br>Less likely to have significant abdominal distension.                  |
| <b>Diagnostic Tests</b>     | Barium enema showing a transition zone.<br>Rectal biopsy confirming absence of ganglion cells.<br>Anorectal manometry may show lack of relaxation of the internal anal sphincter. | Diagnosis is often clinical, based on Rome criteria.<br>Normal barium enema.<br>Normal anorectal manometry.                                                     |

|                              |                                                                                                                            |                                                                                                                                 |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| <b>Treatment</b>             | Surgical removal of the aganglionic segment of the bowel (pull-through procedure).<br>Stoma may be required in some cases. | Dietary modifications (high fiber, fluids).<br>Laxatives or stool softeners.<br>Behavioral therapy.<br>Regular toilet routines. |
| <b>Prognosis</b>             | Good with appropriate surgical treatment.<br>Risk of postoperative complications like enterocolitis.                       | Generally good with appropriate management.<br>Can be a chronic condition in some individuals.                                  |
| <b>Associated Conditions</b> | Often associated with genetic conditions like Down syndrome.<br>Can be part of a syndrome in rare cases.                   | Often associated with psychological or behavioral issues.<br>May be related to diet or lifestyle factors.                       |

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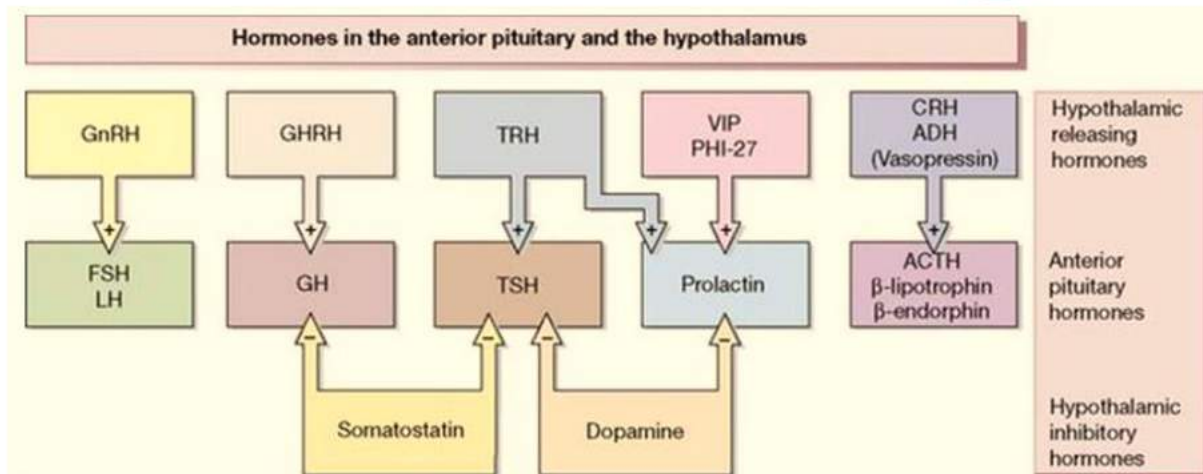
### 8. a) Hypothalamic Pituitary axis.

- ❖ The Hypothalamic-Pituitary Axis is integral to the endocrine system, coordinating a wide range of bodily functions.
- ❖ Its intricate feedback loops and hormone regulation are essential for maintaining physiological balance and responding to internal and external stressors.

#### Hypothalamus:

- **Location:** Part of the brain located just above the brain stem.
- **Function:** Produces releasing and inhibiting hormones that control the release of hormones from the anterior pituitary.
- **Key Hormones:**
  - Corticotropin-Releasing Hormone (CRH)
  - Thyrotropin-Releasing Hormone (TRH)
  - Growth Hormone-Releasing Hormone (GHRH)
  - Gonadotropin-Releasing Hormone (GnRH)
  - Somatostatin (inhibits growth hormone and thyroid-stimulating hormone)
  - Dopamine (inhibits prolactin)





### Pituitary Gland:

- **Location:** Small gland located at the base of the brain.
- **Subdivisions:**
  - **Anterior Pituitary (Adenohypophysis):** Produces and secretes hormones under the regulation of the hypothalamic hormones.
    - Hormones include Growth Hormone (GH), Thyroid-Stimulating Hormone (TSH), Adrenocorticotrophic Hormone (ACTH), Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), Prolactin (PRL).
  - **Posterior Pituitary (Neurohypophysis):** Stores and releases hormones produced by the hypothalamus.
    - Hormones include Oxytocin and Vasopressin (Antidiuretic Hormone, ADH).
- The hypothalamus and pituitary gland are central to the endocrine system, often referred to as the "endocrine orchestra."
- The hypothalamus releases hormones that stimulate or inhibit pituitary hormone release.
- The anterior and posterior pituitary gland hormones, along with their hypothalamic releasing factors, are used in both diagnosis and therapy.
- **Hypothalamic and Anterior Pituitary Hormones:**

- **Corticotropin-Releasing Hormone (CRH):** Used diagnostically to increase ACTH secretion in Cushing's disease and during inferior petrosal sinus sampling to determine the cause of Cushing's syndrome.
- **Adrenocorticotrophic Hormone (ACTH):** Used in the Synacthen tests for diagnosing Addison's disease.
- **Thyrotrophin Releasing Hormone (TRH):** Previously used to test pituitary release of TSH; now used to differentiate between TSHomas and thyroid hormone resistance.
- **Thyroid Stimulating Hormone (TSH):** Controls thyroid hormone synthesis and release; recombinant TSH is used in thyroid cancer treatment.
- **Growth Hormone-Releasing Hormone (GHRH) and Somatostatin:** GHRH stimulates growth hormone secretion, while somatostatin inhibits it. Somatostatin also inhibits secretion of thyrotrophin, insulin, gastrin, and serotonin.
- **Growth Hormone (GH):** Used in treating children with growth hormone deficiency and other conditions like Turner's syndrome, renal failure, Prader-Willi syndrome. In adults, it's used for growth hormone-deficient patients with severely impaired quality of life.
- **Gonadotrophin-Releasing Hormone (GnRH):** Used in the assessment of pituitary function and treatment of infertility.
- **Follicle Stimulating Hormone (FSH) and Chorionic Gonadotrophin (HCG):** FSH stimulates development of ova and spermatozoa, while HCG is involved in spermatogenesis and gonadal testosterone production.
- **Clinical Applications of Pituitary Hormones:**
  - **Growth Hormone in Acromegaly:** Treatment includes surgery and reduction of growth hormone secretion using somatostatin analogues or dopamine agonists.
  - **Pegvisomant:** A growth hormone receptor antagonist used in acromegaly treatment.
  - **GnRH Analogues:** Used to suppress androgen secretion in prostatic carcinoma and in conditions like endometriosis and precocious puberty.
  - **Prolactin:** Secreted by the anterior pituitary, its main function is to stimulate lactation. Hyperprolactinemia can inhibit GnRH.



- **Therapeutic Uses of Hormones:**

- **Vasopressin (Antidiuretic Hormone):** Used for its vasoconstrictor effect in treating oesophageal varices and for its antidiuretic action.
- **Reproductive Hormones:** Includes suppression of oestrogen and/or androgen production in tumour treatment, contraception, fertility treatment, and hormone replacement therapy in post-menopausal women.

- **Special Considerations:**

- The half-life of these polypeptide and glycoprotein hormones is 5-30 minutes, and they are digested if swallowed.
- The use of these hormones and their analogues should generally be in the hands of specialist endocrinologists, oncologists, or gynaecologists due to their complexity and potential side effects.



## 8. b) Passive immunity and its clinical application in paediatric disease.

- ❖ It involves the transfer of active humoral immunity in the form of ready-made antibodies
- ❖ This immunity is short-lived, but it provides immediate protection against various infectious agents
- ❖ Passive immunity plays a vital role in pediatric care, offering immediate but temporary protection against various infectious and autoimmune diseases
- ❖ Its application ranges from standard prophylactic measures in newborns to sophisticated treatments for complex immune disorders
- ❖ The development of new monoclonal antibodies and other immunoglobulin products continues to expand the scope of passive immunity in pediatric therapeutics.

1. **Definition and Mechanism:**

- Passive immunity is the acquisition of antibodies from an external source, as opposed to active immunity where the body produces its own antibodies.
- It can occur naturally, as in the case of maternal antibodies transferred to the fetus through the placenta or to infants through breast milk.
- Artificial passive immunity involves the administration of antibodies, usually in the form of immunoglobulins.

2. **Natural Passive Immunity:**

- **Maternal Antibodies:** Transplacental transfer of IgG antibodies during the third trimester provides neonates with protection against various infections during the first few months of life.
- **Breastfeeding:** Breast milk, especially colostrum, is rich in IgA antibodies and provides mucosal immunity to the infant, protecting against respiratory and gastrointestinal infections.

3. **Artificial Passive Immunity:**

- **Immunoglobulins:** These are preparations containing antibodies, either polyclonal or monoclonal, used to provide immediate protection against specific pathogens.
- **Polyclonal Immunoglobulins:** These include intravenous immunoglobulin (IVIG), which is used in a variety of conditions like immune thrombocytopenia, Kawasaki disease, and as prophylaxis against infections in immunocompromised patients.
- **Monoclonal Antibodies:** These are laboratory-made antibodies that can mimic the immune system's ability to fight off harmful pathogens. They are used in targeted therapies for specific conditions.

4. **Clinical Applications in Pediatric Diseases:**

- **Prophylaxis Against Specific Infections:** For example, RSV (respiratory syncytial virus) immunoprophylaxis in high-risk infants using palivizumab, a monoclonal antibody.
- **Immunodeficiencies:** IVIG is used in children with primary immunodeficiency diseases to prevent recurrent infections.
- **Autoimmune and Inflammatory Conditions:** IVIG is used in Kawasaki disease, a pediatric vasculitis, to reduce the risk of coronary artery aneurysms.



- **Neonatal Infections:** Administration of specific immunoglobulins to neonates exposed to or infected with pathogens like hepatitis B, varicella, or cytomegalovirus.
- **Post-exposure Prophylaxis:** Rabies immunoglobulin in exposed individuals and tetanus immunoglobulin in cases of suspected tetanus exposure.

#### 5. **Advantages and Limitations:**

- **Immediate Protection:** Passive immunity provides immediate defense against an antigen.
- **Short-term Solution:** It does not induce memory; hence, the protection is temporary.
- **Risk of Allergic Reactions:** Especially with IVIG, there is a risk of allergic reactions and other side effects.
- **Cost and Availability:** Some monoclonal antibodies and IVIG can be expensive and not readily available in all settings.

#### 6. **Future Directions:**

- **Monoclonal Antibodies in Infectious Diseases:** There is ongoing research into monoclonal antibodies for prevention and treatment of infectious diseases, especially in immunocompromised children.
- **Gene Therapy:** Potential future applications in generating specific types of passive immunity.

| Aspect                             | Details                                                                                                                                                                                                                     |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Definition</b>                  | Acquisition of active humoral immunity through ready-made antibodies.                                                                                                                                                       |
| <b>Mechanism</b>                   | Transfer of antibodies from an external source, either naturally (maternal antibodies) or artificially (immunoglobulins).                                                                                                   |
| <b>Natural Passive Immunity</b>    | <p><b>Maternal Antibodies:</b> Transplacental transfer of IgG; protection in early infancy.</p> <p><b>Breastfeeding:</b> IgA in breast milk provides mucosal immunity.</p>                                                  |
| <b>Artificial Passive Immunity</b> | <p><b>Immunoglobulins:</b> Polyclonal (e.g., IVIG) and monoclonal antibodies for immediate protection.</p> <p><b>Polyclonal Immunoglobulins:</b> Used in immune thrombocytopenia, Kawasaki disease, immunodeficiencies.</p> |

|                              |                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              | <b>Monoclonal Antibodies:</b> Targeted therapies for specific conditions.                                                                                                                                                                                                                                                                                               |
| <b>Clinical Applications</b> | <b>Prophylaxis Against Infections:</b> e.g., RSV immunoprophylaxis in infants.<br><b>Immunodeficiencies:</b> IVIG in primary immunodeficiency.<br><b>Autoimmune Conditions:</b> IVIG in Kawasaki disease.<br><b>Neonatal Infections:</b> Specific immunoglobulins for hepatitis B, varicella, CMV.<br><b>Post-exposure Prophylaxis:</b> Rabies, tetanus immunoglobulin. |
| <b>Advantages</b>            | Immediate protection against antigens; crucial in early infancy and for immunocompromised patients.                                                                                                                                                                                                                                                                     |
| <b>Limitations</b>           | Temporary protection; no induction of memory. Risk of allergic reactions. Cost and availability issues.                                                                                                                                                                                                                                                                 |
| <b>Future Directions</b>     | Research into monoclonal antibodies for infectious diseases; potential applications in gene therapy.                                                                                                                                                                                                                                                                    |

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### 9. a) Indications of CSF manometry in children.

- ❖ Cerebrospinal fluid (CSF) manometry in children is an important diagnostic procedure used to measure the pressure of the cerebrospinal fluid
- ❖ This test is crucial in diagnosing and managing various neurological conditions
- ❖ CSF manometry is a valuable tool in pediatric neurology, providing essential information for the diagnosis and management of a wide range of conditions affecting the central nervous system
- ❖ Its use should be guided by clinical indications and performed by experienced healthcare professionals due to the invasive nature of the procedure.

#### 1. **Increased Intracranial Pressure (ICP):**

- Suspected intracranial hypertension.
- Monitoring and management of conditions like hydrocephalus.
- Evaluation of shunt function in children with ventriculoperitoneal shunts.

#### 2. **Infectious Diseases:**

- Suspected meningitis or encephalitis.
- Evaluation of response to treatment in bacterial, viral, or fungal CNS infections.



3. **Neurological Disorders:**

- Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri.
- Chiari malformation and other structural abnormalities.
- Assessment of CSF flow dynamics.

4. **Autoimmune and Inflammatory Conditions:**

- Suspected central nervous system (CNS) involvement in autoimmune diseases like lupus, sarcoidosis.
- Evaluation of demyelinating diseases like multiple sclerosis.

5. **Subarachnoid Hemorrhage:**

- Diagnosis in cases where CT scan is inconclusive.
- Monitoring for complications like hydrocephalus or vasospasm.

6. **Neoplastic Diseases:**

- Evaluation of CNS involvement in leukemia or lymphoma.
- Monitoring for metastasis in children with known malignancies.

7. **Traumatic Brain Injury:**

- Assessment and monitoring of ICP after severe head trauma.
- Evaluation of CSF leaks or intracranial hematomas.

8. **Diagnostic Lumbar Puncture:**

- CSF manometry is often performed as part of a diagnostic lumbar puncture to measure opening pressure.
- Useful in diagnosing conditions like Guillain-Barré syndrome or normal pressure hydrocephalus.

9. **Therapeutic Interventions:**

- Therapeutic lumbar puncture in conditions like IIH.
- CSF drainage in cases of acute hydrocephalus.

10. **Postoperative Monitoring:**

- In children undergoing neurosurgery, especially for hydrocephalus or brain tumors.

### 11. *Research and Clinical Trials:*

- CSF manometry may be used in clinical trials or research studies to understand the pathophysiology of various neurological conditions.

| <b>Indication</b>                             | <b>Diagnostic and Decision-Making Utility of CSF Manometry</b>                                                                   |
|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Increased Intracranial Pressure (ICP)</b>  | Measures elevated CSF pressure.<br>Assists in diagnosing hydrocephalus, guiding shunt placement, and assessing shunt function.   |
| <b>Infectious Diseases</b>                    | Confirms elevated pressure in meningitis/encephalitis.<br>Helps in monitoring the effectiveness of treatment for CNS infections. |
| <b>Neurological Disorders</b>                 | Diagnoses conditions like IIH.<br>Assesses CSF dynamics in structural abnormalities like Chiari malformation.                    |
| <b>Autoimmune and Inflammatory Conditions</b> | Indicates CNS involvement in systemic autoimmune diseases.<br>Aids in the diagnosis of demyelinating diseases.                   |
| <b>Subarachnoid Hemorrhage</b>                | Detects changes in CSF pressure indicative of hemorrhage.<br>Monitors for complications like hydrocephalus.                      |
| <b>Neoplastic Diseases</b>                    | Assists in evaluating CNS involvement in hematological malignancies.<br>Monitors for metastasis in known malignancies.           |
| <b>Traumatic Brain Injury</b>                 | Monitors ICP post-injury.<br>Helps in assessing CSF leaks or hematomas.                                                          |
| <b>Diagnostic Lumbar Puncture</b>             | Measures opening pressure.<br>Essential in diagnosing conditions like Guillain-Barré syndrome or normal pressure hydrocephalus.  |
| <b>Therapeutic Interventions</b>              | Assists in therapeutic lumbar punctures for conditions like IIH.<br>Guides CSF drainage in acute hydrocephalus.                  |
| <b>Postoperative Monitoring</b>               | Monitors ICP in post-neurosurgical patients.<br>Essential for postoperative care in hydrocephalus or brain tumor surgeries.      |
| <b>Research and Clinical Trials</b>           | Used in studies to understand the pathophysiology of neurological conditions.<br>Helps in developing new treatment strategies.   |

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## 9. b) Ventriculoperitoneal shunt in children.

- ❖ Ventriculoperitoneal shunting is a life-saving procedure for children with hydrocephalus and other conditions causing increased intracranial pressure
- ❖ While it carries risks of complications, advancements in shunt technology and careful postoperative management have greatly improved outcomes for these patients
- ❖ Regular monitoring and multidisciplinary care are essential for the long-term well-being of children with VP shunts.

### A. **Indications:**

- Hydrocephalus of various etiologies, including congenital, post-infectious, post-hemorrhagic, and obstructive causes.
- Conditions leading to CSF flow obstruction, like tumors or cysts.
- Selected cases of idiopathic intracranial hypertension (IIH).

### B. **Components of a VP Shunt:**

- **Ventricular Catheter:** Inserted into a lateral ventricle of the brain.
- **Valve Mechanism:** Regulates CSF flow to prevent over- or under-drainage. Valves can be fixed or programmable.
- **Peritoneal Catheter:** Extends from the valve to the peritoneal cavity, where CSF is absorbed.

### **Types of shunts:**

#### 1. **High-Flow Shunts:**

- Designed to drain CSF at a higher rate.
- Typically used in situations where there is a need for rapid reduction of intracranial pressure (ICP) or in cases of high CSF production.
- May be more appropriate in acute settings or in certain types of hydrocephalus with significantly elevated CSF volume or pressure.
- Risk: Potential for overdrainage, leading to complications such as subdural hematomas or slit ventricle syndrome.

#### 2. **Low-Flow Shunts:**

- Drain CSF at a slower, more controlled rate.
- Often used in chronic management of hydrocephalus where gradual CSF drainage is preferred.
- Helps in minimizing the risks associated with rapid changes in intracranial pressure.
- Particularly useful in patients with normal pressure hydrocephalus (NPH) or those at risk of overdrainage complications.

### 3. **Adjustable (Programmable) Shunts:**

- Can be set to function as either high-flow or low-flow based on the patient's needs.
- The flow rate can be adjusted non-invasively using a magnetic device.
- Offers flexibility in managing varying CSF dynamics and patient-specific requirements over time.
- Ideal for patients whose CSF drainage needs may change, such as growing children or those with fluctuating intracranial dynamics.

### 4. **Gravity-Assisted Shunts:**

- Incorporate a mechanism that adjusts flow based on the patient's position.
- Designed to prevent overdrainage when the patient is upright.
- Can be considered a subset of low-flow shunts as they primarily aim to control the rate of drainage in different body positions.

### C. **Procedure:**

- Performed under general anesthesia.
- A small hole is drilled in the skull, and the ventricular catheter is passed into a ventricle.
- The catheter is connected to the valve, which is often placed behind the ear.
- The peritoneal catheter is tunneled under the skin to the abdomen and inserted into the peritoneal cavity.

### D. **Postoperative Care:**



- Monitoring for signs of infection, shunt malfunction, and adequate CSF drainage.
- Regular follow-ups for shunt adjustments, especially in growing children.

**E. Complications:**

- **Infection:** Most common in the first few months post-surgery.
- **Shunt Malfunction:** Blockage or disconnection of the catheter, requiring revision surgery.
- **Overdrainage/Underdrainage:** Leading to symptoms like headaches, vomiting, or altered consciousness.
- **Abdominal Complications:** Including peritonitis or hernias.

**F. Long-Term Considerations:**

- Many children require shunt revisions during their lifetime.
- Lifelong follow-up is necessary to monitor for complications and assess shunt function.

**G. Advancements in Shunt Technology:**

- Programmable valves allow non-invasive adjustments to the rate of CSF drainage.
- MRI-compatible shunts reduce the risk of malfunction during imaging studies.

**H. Quality of Life:**

- VP shunts significantly improve the quality of life in children with hydrocephalus.
- Early intervention and regular follow-up are key to successful outcomes.

**I. Educational and Developmental Support:**

- Children with hydrocephalus may require educational and developmental interventions due to potential cognitive and motor delays.

-----X-----X-----

## 10. a) Molecular diagnostic parameters in the diagnosis of acute myeloid leukemia.

*(These types of questions are really difficult to recollect and answer in the exam, but unfortunately the trend of one question in each paper has started; Similar question on CFTR mutation classification recurred in subsequent paper)*

- ❖ The diagnosis of Acute Myeloid Leukemia (AML) has increasingly incorporated molecular diagnostic parameters, which provide critical insights into the disease's subtype, prognosis, and potential therapeutic targets
- ❖ The integration of these molecular diagnostic parameters into the clinical evaluation of AML represents a significant advancement in personalized medicine
- ❖ It not only aids in the accurate classification and prognosis of AML but also guides the selection of targeted therapies, contributing to improved patient outcomes
- ❖ Molecular diagnostics in AML is a rapidly evolving field, with ongoing research continually refining our understanding of the disease's molecular underpinnings.

### 1. **Gene Mutations:**

- **FLT3 (Fms-like tyrosine kinase 3):** Mutations, especially internal tandem duplications (ITD), are common in AML and associated with a poor prognosis.
- **NPM1 (Nucleophosmin):** Mutations are often found in AML and, in the absence of FLT3-ITD, can indicate a better prognosis.
- **CEBPA (CCAAT/enhancer-binding protein alpha):** Biallelic mutations are associated with a favorable prognosis.
- **RUNX1 (Runt-related transcription factor 1):** Mutations are associated with a poor prognosis.

### 2. **Chromosomal Abnormalities:**

- **t(8;21)(q22;q22.1); RUNX1-RUNX1T1**
- **inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11**
- **t(15;17)(q24.1;q21.2); PML-RARA** (associated with acute promyelocytic leukemia, a subtype of AML)
- Complex karyotypes and certain chromosomal deletions are associated with a poor prognosis.



### 3. **Epigenetic Changes:**

- **DNMT3A (DNA methyltransferase 3 alpha):** Mutations are common in AML and can influence treatment response and prognosis.
- **IDH1 and IDH2 (Isocitrate dehydrogenase 1 and 2):** Mutations are associated with distinct metabolic abnormalities and can be targeted by specific inhibitors.

### 4. **Gene Expression Profiling:**

- Advanced techniques like RNA sequencing can identify unique gene expression patterns that may have prognostic or therapeutic implications.

### 5. **Minimal Residual Disease (MRD) Assessment:**

- Techniques like flow cytometry and PCR are used to detect residual leukemic cells after treatment, which is crucial for prognosis and guiding further therapy.

### 6. **Next-Generation Sequencing (NGS):**

- Allows for the comprehensive analysis of multiple genetic abnormalities simultaneously.
- Can identify novel mutations and provide a more personalized approach to treatment.

### 7. **BCR-ABL1 Fusion Gene:**

- While more commonly associated with Chronic Myeloid Leukemia (CML), the presence of the Philadelphia chromosome (BCR-ABL1 fusion gene) in AML is critical for diagnosis and treatment, as it may respond to tyrosine kinase inhibitors.

### 8. **TP53 Mutations:**

- Associated with complex karyotypes and a poor prognosis.

-----X-----X-----

## 10. b) **Indications of Rituximab in pediatric diseases.**

- ❖ Rituximab's role in pediatric diseases is primarily as a second-line or adjunctive therapy, particularly in conditions where B-cell activity plays a significant role.
- ❖ Its use must be carefully weighed against potential risks, including infusion reactions, infections, and long-term B-cell depletion.

- ❖ The decision to use rituximab should be based on a comprehensive assessment of the patient's condition, response to previous treatments, and overall health status.

### **Drug Class**

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen found on the surface of B-lymphocytes. It belongs to the class of anti-CD20 monoclonal antibodies.

### **Mechanism of Action**

- The drug works by binding to the CD20 antigen on B cells, leading to B cell lysis. This action can deplete B cells from the circulation, thereby modulating the immune response.
- The mechanisms of cell lysis include complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, and induction of apoptosis.

### **Indications in Children**

- Autoimmune Hemolytic Anemia (AIHA)
- Juvenile Idiopathic Arthritis (JIA)
- Nephrotic Syndrome
- B-cell lymphomas like Non-Hodgkin's Lymphoma

| <b>Disease/Condition</b>                                           | <b>Indication for Rituximab</b>                                                                             |
|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| <b>B-cell Non-Hodgkin Lymphoma</b>                                 | First-line and relapsed/refractory treatment.<br>Part of combination chemotherapy regimens.                 |
| <b>B-cell Acute Lymphoblastic Leukemia (ALL)</b>                   | Relapsed or refractory cases.<br>Often used in combination with chemotherapy.                               |
| <b>Chronic Immune Thrombocytopenic Purpura (ITP)</b>               | Second-line treatment for steroid-resistant ITP.<br>Used in cases not responding to conventional therapies. |
| <b>Rheumatoid Arthritis</b>                                        | Severe, treatment-resistant cases.<br>Often used in combination with methotrexate.                          |
| <b>Systemic Lupus Erythematosus (SLE)</b>                          | Severe, refractory cases, particularly with renal involvement.<br>Used when conventional therapies fail.    |
| <b>Granulomatosis with Polyangiitis (Wegener's Granulomatosis)</b> | Severe disease or disease refractory to standard therapy.<br>Used in combination with corticosteroids.      |
| <b>Microscopic Polyangiitis</b>                                    | For induction of remission in severe or refractory cases.                                                   |



|                                                                   |                                                                                                                               |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
|                                                                   | Combined with corticosteroids.                                                                                                |
| <b><i>Nephrotic Syndrome</i></b>                                  | Steroid-dependent or steroid-resistant cases.<br>Particularly in minimal change disease and FSGS.                             |
| <b><i>Autoimmune Hemolytic Anemia</i></b>                         | Second-line treatment for cases not responding to steroids or splenectomy.<br>Especially in warm antibody type.               |
| <b><i>Post-Transplant Lymphoproliferative Disorder (PTLD)</i></b> | Used in EBV-associated PTLD.<br>Often part of a reduced-intensity chemotherapy regimen.                                       |
| <b><i>Refractory Dermatomyositis and Polymyositis</i></b>         | Used in cases not responding to steroids and other immunosuppressants.<br>Especially with severe muscle or skin involvement.  |
| <b><i>Refractory Myasthenia Gravis</i></b>                        | Used in severe cases not responding to conventional therapy.<br>Aimed at reducing antibodies against acetylcholine receptors. |
| <b><i>Pemphigus Vulgaris</i></b>                                  | Severe or refractory cases.<br>Used when steroids and other immunosuppressants are ineffective.                               |
| <b><i>Refractory Evans Syndrome</i></b>                           | Used in cases not responding to steroids, IVIG, or splenectomy.<br>Targets autoimmune hemolytic anemia and ITP.               |
| <b><i>Hemophagocytic Lymphohistiocytosis (HLH)</i></b>            | Used in refractory or relapsed HLH.<br>Part of the HLH-94/HLH-2004 treatment protocols.                                       |

**Dosage:** Varies depending on the condition being treated.

- B-cell lymphomas, the typical dosage is 375 mg/m<sup>2</sup> administered intravenously once a week for four weeks
- For autoimmune conditions like AIHA or JIA, the dosage is often 375 mg/m<sup>2</sup> IV once, but this can vary

### **Side Effects**

The drug is generally well-tolerated but can have some side effects, including:

- Infusion reactions: Fever, chills, and rigors are common during or after the infusion.
- Infections: Being an immunosuppressive agent, Rituximab increases the risk of bacterial, viral, and fungal infections.
- Hepatitis B reactivation: Patients should be screened for Hepatitis B virus before initiation of therapy.

- Myelosuppression: Reduced levels of blood cells can occur, requiring regular blood count monitoring.

### Special Considerations

- Pre-medication with antihistamines and antipyretics is often recommended to minimize infusion reactions.
- Hepatitis B and C serology should be checked before starting treatment.
- Contraindicated in patients with severe heart failure or hypersensitivity to the drug or its components.

